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November 23, 2008

Spencer D. Ault, Esquire
The Law Office of Spencer D. Ault, Esquire
Stone Manor Associates
13193 Mountain Road
Lovettsville, VA 20180 re: Janelle Bailey Boroday Hill and Savannah Anne Hill

Dear Mr. Ault:

The records regarding the management of the above-named patient were re-reviewed; the following conclusions have been drawn to a reasonable degree of medical probability.

Key points established in the 10/16/2008 Expert Report were as follows:

> It traced the key-facts in this case through a series of analytic "hoops" that can be accessed expeditiously by noting the "(first page)" of each of the concepts discussed: Standing (1), Database (3), Assertions (6), Narrative (6), Medical Malpractice Issue Components (16), Baby Savannah Short-Term Sequellae (16), Baby Savannah Long-Term Sequellae (32), Depositions (32), Aventis-written PPI (35), Recapitulation of Medical Malpractice Issue Components (37), Cocaine (37), Periventricular Leukomalacia (38), Alternative Anticoagulants (40), Theory of the Case Against Aventis (42), Monitoring (42), Current PPI (72), Aventis Toxicity Files (75), Cross-Reference of Files and Internal Analysis Pages (81), Distillation (116), Distillation of Distillation (124), Theorizing (126), Marketing & Promotion (127), and Amended Motion for Judgment (130).

Key observations made while generating this report were as follows:

> Aventis promoted the use of Lovenox, despite the fact that it had been the presumptive etiology of multiple episodes of neonatal hemorrhage—causing both death and disability—which were otherwise unexplained. There is no evidence that receipt of adverse drug reaction ["ADR"] data prompted Aventis to investigate additional potential toxicity cases; indeed, the pathological placental changes [when known] were not consistent with the major differential-diagnostic consideration, *abruptio placentae*. Regardless, the initial decision to initiate Lovenox was made by Dr. Khan, whose conduct was informed by the information disseminated by Aventis.

The focus has been less on the obstetrical issues and the basic science than on the hematologic findings; theorizing has been dutifully preserved, but definitive decisions cannot antedate detailed pharmacologic assessment. Emphasized, also, has been the view that Savannah did not suffer any type of congenital anomaly; rather, the intracerebral hemorrhage caused her multiple neurological disabilities due to Periventricular Leukomalacia. Because the baby was small-for-age and the placenta was abnormal, hemorrhage was not acute; placental vascular thrombosis is provoked by a Diffuse Intravascular Coagulation ["DIC"] which yields a combination of bleeding/clotting due, in part, to consumption of procoagulant proteins.

Use of alternative agents and the potential to monitor Lovenox activity (using tests such as Anti-Xa, Enox and ACT) has been reviewed in-detail. Specifically, other agents that have not been shown to cross the placenta exist and Lovenox monitoring was available and validated; also, Xa-ACT is superior to the conventional ACT for the bedside monitoring of LMWH anticoagulation and Lovenox affects AT-III, Xa, and other molecules.

Assessment: What is particularly remarkable both in this physician's distillation and the tabular presentation of the data is the absence of a consistent database. For example, pathologic assessment of the placenta is not consistently reported, and this is information that could have been acquired in "real time" when reports of adverse actions arrived. Even if other explanations for any given finding might be conjured—such as a conjoint "abruption placenta"—the inability to "reach" even this rudimentary level of analysis impugns the ability to claim that the public-protection role of the pharmaceutical house has been upheld. This is not a pass-through activity; rather, it is to be based on the best measured judgments regarding the need to maintain an academic/clinical level of inquiry that would not wish to miss any potentially-toxic drug-effect. That the public trust in the FDA is predicated on the maxim "*primum non nocere*" ["the first priority is to do no harm"] is central to its basic charge; efficacy data are accrued and reported, but toxicity data are emphasized.

Due to variable numbering systems and data summaries that appeared to omit cases, it was not always possible to assume that comparable case-presentations overlapped. That some cases were dismissed by anonymous physicians is also grist for probing, for the desire to engage in professional denial can blind investigators from unearthing facts. This would define why some findings were "expected" and why classification of symptoms/ syndromes supplanted the need to distill precise findings/diagnoses.

Clearly, any pregnant woman who has been anticoagulated is intuitively at increased risk to develop obstetrical complications, due either to the underlying diagnosis/diagnoses that had prompted this medicinal intervention or to potential iatrogenic complications.

Review of the Aventis database yielded this Distillation of Distillation [abbreviated]:

> These 31 assessments focus on two broad categories of concern raised by this exhaustive review of the Aventis files related to Lovenox. The first is evidence of transplacental transmission of this drug, perhaps associated with an exaggerated fetal-maternal leak… and perhaps a distinct phenomenon; offering potential physiologic explanations is not the proper role of this medical expert. The second is evidence that there was no follow-up of additional reports of potential transplacental transmission of this drug, with particular note of the absence of a focus on the need to examine the placenta pathologically; again, conjuring alternative obstetrical explanations (*e.g.*, ascribing anything adverse to *abruptio placentae*, spontaneous abortion, or an occult congenital/developmental anomaly) is not the proper role of this medical expert, particularly when provided such paltry data.
>
> Entire categories of information could not be analyzed, such as the dosage employed and whether any of the recognized monitoring tests were actually applied (either in a clinical or in a research setting). For example, **AVE008506** [cited at the bottom of page 116] mirrors the instant case. And in one instance [**AVE 008519**], neonatal thrombocytopenia suggested the potential for Lovenox to have previously crossed the placenta. In another instance [**AVE 008530**], neonatal hemorrhage (intrathoracic) again suggested transplacental drug transmission. Another case [**AVE 010009**] revealed widespread hemorrhage that was antedated by a retroplacental hematoma, again suggesting that the primary event was caused by the transplacental transmission of this drug (indirectly leading to the death of the fetus). And one final case [**AVE 010135**] revealed a fetus had died from hemoperitoneum, again suggesting that the primary event had been transplacental drug transmission.
>
> <u>These five cases are on-point, but nowhere in the Aventis filings are they aggregated. Further, many additional cases require a modicum of follow-up; they have not been tabulated here because of uncertainty regarding whether there is significant overlap. Others require clarification regarding the status of the placenta—as referenced *supra*—because it is necessary to deal in particular with the inclusion of at least one other state (*abruptio placentae*) within the differential diagnosis of subsequent fetal demise. And still others require investigation as to how Aventis did or did not choose to follow-up; adopting a passive role consistently through this process appears to have been a pattern.</u>
>
> Not to be inappropriately married to one's own particular statement expressing a sense of feeling aghast at what had been unearthed, re-restated is this reaction to the unfulfilled need for basic due diligence when a pharmaceutical house is engaged in self-scrutiny.

> Although this section appears to have been composed in conclusory language, it is felt that its contents—particularly those that have been underlined—flow inevitably from the database without insertion of editorialization. On the other hand, knowledge of the role of the FDA (and charge from the FDA to *inter alia* Aventis) was invoked as indicated.
>
> The direct result of the dissemination of such information would have been that Dr. Khan would have either chosen another agent or employed a monitoring test (if dosages would be affected by the assessment of additional information regarding its effects); either way, potential toxicity to mother/fetus would have been precluded and/or ameliorated. Also, as discussed *supra*, it is clear that the permanent effects upon the baby (Savannah)—intracranial hemorrhage causing global developmental delays, cerebral palsy, seizures, auditory processing disorders, deafness, and blindness—have stressed-out the patient.
>
> One frame of reference used is whether the accumulated data regarding hematologic toxicity met or exceeded that which had prompted Aventis to have issued a boxed-warning regarding a risk of spinal hematoma (following 19 case-reports). Again, correlative is whether such data should have prompted Aventis to have recommended use of a monitoring test (or, at the very least, have studied the potential for this approach).
>
> The specific pathological changes associated with *abruptio placentae* [*see* page 124] were not noted in the instant case [*see* page 9].

And it was recognized that there are these other types of low-molecular-weight-heparins:

> *LOVENOX Therapeutic Class defined as a market basket consisting of:
> Lovenox® (enoxaparin sodium) Injection
> Fragmin® (dalteparin sodium) – a registered trademark of Pharmacia Corporation
> Normiflo® (ardeparin sodium) – a registered trademark of American Home Products
> Orgaran® (danaparoid sodium) – a registered trademark of N.V. Organon Corporation
> Innohep® (tinzaparin sodium) – a registered trademark of Leo Pharmaceutical Products Ltd.
> Arixtra® (fondaparinux sodium) – a registered trademark of Sanofi-Synthelabo Inc.

No effort has been made to review/compare/contrast the literature generated by study of these other agents; the focus herein has remained trained upon Lovenox (of Aventis).

The most recent PDR-entry regarding Lovenox by Aventis contains these key-phrases:

> *Pregnancy: Pregnancy Category B*
> All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Lovenox's potential to increase the risk of developmental abnormalities above background risk.
>
> *Fetal Risk Summary*
> Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.
>
> *Clinical Considerations*
> It is not known if dose adjustment or monitoring of anti-Xa activity of enoxaparin are [sic; should be "is"] necessary during pregnancy.
>
> Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves, and those with inherited or acquired thrombophilias, also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used. [Under "data" *infra*: "A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves has been conducted."]
>
> All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches (see BOXED WARNING, SPINAL/EPIDURAL HEMATOMAS).
>
> Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.
>
> *Human Data*
> There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been post marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

Animal Data
Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m 2 /day and 410 mg/m 2 /day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

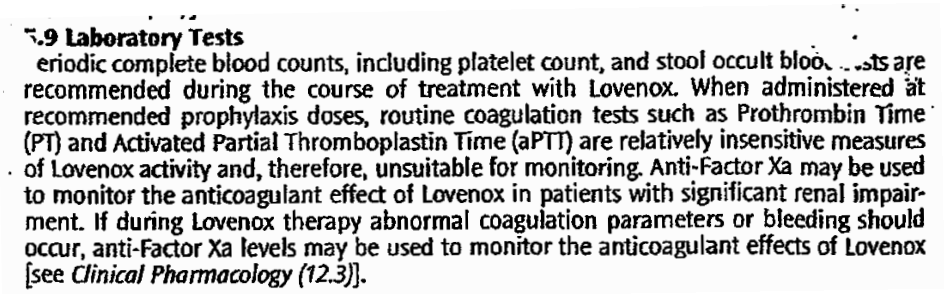
During March, 2002, Aventis sent a letter to Health Professionals stating:

> *Non-teratogenic Effects*: There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

This was how the aforementioned data were previously conceptualized:

> Noting that Aventis had consistently advised against the need to perform monitoring labs, its advice that "pregnant women receiving enoxaparin should be carefully monitored" cries for elaboration for, as a stand-along sentence, it is absolutely meaningless…even were it to be perceived as a "disclaimer." [How should this monitoring occur? Which test is advised? How often should it be acquired? Would dosage be affected?]

Although a publication issued in 2007 obviously would not have affected what doctors did or didn't know a half-decade prior, noting the information provides insight as to the contents of what might have been issued years previously. Thus, if the information here is based on old data, it should have been captured in old documents (which it wasn't), to wit:



5.9 Laboratory Tests

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox in patients with significant renal impairment. If during Lovenox therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox [see *Clinical Pharmacology (12.3)*].

Fetal Risk Summary

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Clinical Considerations

It is not known if either dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see *Warnings and Precautions (5.7) and Use in Specific Populations (8.6)*]. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches [see *Boxed Warning*]. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data

•*Human Data* - There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

Of-interest is a 6/15/2002 article from *OB/GYN News* that summarized the posture that was most favorable to Aventis; the most absolute level of reassurance was as follows:

But according to Dr. Charles Lockwood, the revised label should not prevent physicians from using the drug in most pregnant women. "There is no reason to change practice in any way except to avoid low molecular weight heparin in women with mechanical prosthetic heart valves," said Dr. Lockwood, professor and chair of obstetrics and gynecology at New York University, New York.

"The agent does not cross the placenta, providing no biological plausibility for such a risk. Secondly, a large study by Dr. J. Lepercq and associates [BJOG 108(11):1134-40, 2001] described pregnancy outcomes in 604 women treated with enoxaparin and observed a congenital anomaly rate of only 2.5%. And lastly, the variety of anomalies reported by Aventis and their rare occurrence strongly suggests no specific malformation pattern or increased frequency," he said.

These analytic points were cross-walked successfully with the Complaint's allegations:

36. Aventis was negligent in the following particulars:

a. Aventis is promoting this drug for use in pregnancy despite the fact that there are no adequate and well-controlled studies of safety in pregnant women;

b. Aventis has failed to provide adequate warnings of the risks of using Lovenox during pregnancy, even though there have been post marketing reports of fetal deaths when pregnant women received Lovenox injections.

c. Aventis has been negligent in the design, testing, manufacture and marketing of Lovenox;

d. Aventis has been negligent in that they have provided a package insert that is confusing and contradictory;

e. Aventis has been negligent is leading doctors to believe that no testing is necessary to monitor pregnant women who are receiving Lovenox; and

f. Aventis has not provided adequate information to doctors prescribing Lovenox to pregnant women for them to know how or when to prescribe Lovenox and to know how to monitor the safety of Lovenox during pregnancy.

Regarding each of these specific assertions, the following conclusions have been drawn regarding the conduct of Aventis with regard to the use of Lovenox in pregnant women:

a. It is promoted absent adequate and well-controlled safety studies.

b. There are no adequate warnings as to its risk, despite the existence of post-marketing reports of fetal deaths.

c. There has been negligence in its design, testing, manufacture and marketing.

d. The patient package insert is confusing and contradictory.

e. Doctors have been led to believe that monitoring tests are not needed.

f. Doctors have not been educated regarding the indications for and monitoring of its use.

These points were illustrated in the following fashion:

> There is no doubt that it has been promoted as being safe in pregnant women; indeed, the most current recommendations only exclude those with artificial heart valves. There have been no safety studies thereof. The warnings do not capture the essence of the information provided via case-reports, even those that are marginally complete when depicting fetal deaths; even if only one was related to another diagnosis (*abruptio placentae*), there was an obligation to convey the existence of any such "differential diagnosis" to the practitioner, thereby arming him/her with necessary information that would then be included within the Informed Consent process when dealing with the patient. Negligence in the acquisition, follow-up and analysis of post-marketing case reports necessarily affects adversely the methodology employed when designing and implementing its promotion, when advising which tests might be best employed when monitoring its use, when manufacturing an optimal agent for anticoagulation in this high-risk patient group, and when promoting its use therein. The evolving patient-package-insert ["PPI"] does not capture the necessary information, and certain sections are either/both confusing/contradictory when (for example) advising that pregnant women be "monitored." Physicians have been constantly reassured that this agent is immediately effective and need not be monitored, despite the existence of available tests that could—particularly in a high-risk population—ameliorate toxicity. Overall, physicians have not been informed as to its proper use and monitoring in the high-risk population of pregnant women, with particular regard to the need to decrease the risk of neonatal hemorrhage (not withstanding potential obstetrical delays).

This summary of the highlights of the initial Expert Report segues into tasks that emerge.

The following Aventis Pharmaceuticals Filings also serve as the basis for this report:

Adverse Event Reports [1/2/1994 – 11/5/2007]
Advertising Reports [6/9/2003 – 2/7/2008] {these corroborated prior views}

The following FDA Filings also serve as the basis for this report:

#1- MB37_GCI10_SA_Book_765_V1of2_prgnt_wmn_full_lit.pdf
#2- MB37_GCI10_SA_Book_765_V1of2_AE_rvw_in_prgnt_wmn.pdf
#3- MB37_GCI10_SA_Book_765_V1of2_AE_prgncy_stdy_clin_doc.pdf
#4- MB38_GCI11_SA_Book_766_V2of2_prgncy_stdy_narratives.pdf

An Adverse Event Review (1/1/1987 – 6/15/2000) was correlated with other data [#1].

A full set of publications (as of 9/12/2000) was correlated with other data [#2].

Clinical documentation (also as of 9/12/2000) was correlated with other data [#3].

More Patient Narratives [AVE 004988 – 505005] were reviewed [#4, Book 766, *supra*]. To whatever degree they might correlate with prior renditions has not been determined. This is the listing from 9/12/2000, termed a "retrospective study" [Aventis Book #766].

What has not been reviewed is the overall context of the FDA's assessment of this agent. The IND has not been studied, in conjunction with animal trials and pharmacokinetics, thereby not yielding the capacity to adjudge the claim that Lovenox does not cross into the fetal circulation via the placenta. It may be recalled the initial Expert Report had a summary of such theorizing (as postulated by others) and, therefore, whether it is now viewed as necessary that fetal-maternal circulation breaches antedate generation of IgG… this type of consideration is deferred because summarizing known data is a priority.

It is not surprising that a report be requested that is based on defined-but-limited data, for the FDA File is undoubtedly quite large. Nevertheless, there remains a definable "medical component" to the need to review all internal memos and correspondences—both of FDA and Aventis—to gain an appreciation of how the aforementioned database had been assessed by all responsible parties, recognizing that (from prior medicolegal experience) individuals who have been accused of wrongdoing will invoke subsequent deposition-assertions when averring that such charges have been made prematurely and without consideration of the context in which these professionals had been functioning.

This is particularly vital with regard to how these two entities interacted over the decades. The broader implications (such as how other pharmaceutical companies were behaving) themselves carry Public Health import [as documented in myriad FDA mandates, *infra*] which impact upon the justification for the citizenry to trust that fiscal motives are not at-play when (for example) monitoring the anti-Xa (despite prior establishment of norms) is not formally recommended. Otherwise, the "marketing/promotion" component of the database isn't scrutinized herein; the focus remains on how Lovenox affected pregnancy.

It is now necessary to continue to compile the data that were acquired from Aventis. [The indexing system that has been used herein is again tethered to the raw data, with potential implications distilled independently.] It is also necessary to compile the outcome of serial decision-making activity by Aventis regarding how these data were to be processed internally and then portrayed externally. Again, whatever transpired is to be "processed" in a fashion that is both disinterested and comprehensive. To maintain consistency of the numbering-system employed, this continues the listing @ "41."

Thus, this initial outline is drawn directly from the "Full ADR Index" for Binders 11-12.

1/2/2004 – 5/26/2004

41.	Pregnancy related ADR	[AVE 010179]
	Pregnancy related ADR	[AVE 010182]
	Fetal death ADR	[AVE 010184]
	Pregnancy related ADR	[AVE 010188]
	Litigation related ADR	[AVE 010190]
	Pregnancy related ADR	[AVE 010192]
	Pregnancy related ADR	[AVE 010194]
	Pregnancy related ADR	[AVE 010196]
	{MASTER BINDER 11:ADR 4, Section J}	

5/27/2004 – 8/31/2004

42.	Pregnancy related ADR	[AVE 010199]
	Pregnancy related ADR	[AVE 010201]
	Fetal related ADR	[AVE 010203]
	Pregnancy related ADR	[AVE 010205]
	Pregnancy related ADR	[AVE 010207]
	Pregnancy related ADR	[AVE 010210]
	Pregnancy related ADR	[AVE 010212]
	Pregnancy related ADR	[AVE 010214]
	Pregnancy related ADR	[AVE 010216]
	Pregnancy related ADR	[AVE 010218]
	{11:4,K}	

9/1/2004 – 12/31/2004

43.	Pregnancy related ADR	[AVE 010221]
	Pregnancy related ADR	[AVE 010223]
	Pregnancy related ADR	[AVE 010226]
	Pregnancy related ADR	[AVE 010231]
	Pregnancy related ADR	[AVE 010234]
	Pregnancy related ADR	[AVE 010238]

Pregnancy related ADR [AVE 010242]
Pregnancy related ADR [AVE 010245]
Pregnancy related ADR [AVE 010250]
Pregnancy related ADR [AVE 010254]
{11:4,L}

1/3/2005 – 3/31/2005

44. Pregnancy related ADR [AVE 010257]
Pregnancy related ADR [AVE 010257]
Pregnancy related ADR [AVE 010259]
Pregnancy related ADR [AVE 010261]
Pregnancy related ADR [AVE 010264]
Pregnancy related ADR [AVE 010266]
Pregnancy related ADR [AVE 010269]
Pregnancy related ADR [AVE 010271]
{11:4,M}

45. Abstract: **Enoxaparin Treatment in 600 Pregnancies in Women with Pregnancy Loss and Thrombophilia** [Author: A. Sarto]
Source: JTH 2003; 1 Supplement 1 p.1898
[AVE 010277]

Pregnancy related ADR [AVE 010279]
Pregnancy related ADR [AVE 010281]
{11:4,N}

4/1/2005 – 5/26/2005

46. Pregnancy related ADR [AVE 010284]
Pregnancy related ADR [AVE 010286]
Pregnancy related ADR [AVE 010288]
Pregnancy related ADR [AVE 010291]
Pregnancy related ADR [AVE 010293]
Pregnancy related ADR [AVE 010295]

Duplicate copy of:
Abstract: **Enoxaparin Treatment in 600 Pregnancies in Women with Pregnancy Loss and Thrombophilia** [Author: A. Sarto]
Source: JTH 2003; 1 Supplement 1 p.1898
[AVE 010304]
{11:4,O}

5/27/2005

47.	Pregnancy related ADR	[AVE 011943]
	Pregnancy related ADR	[AVE 011947]
	{11:4,P}	

5/28/2005 – 10/28/2005

48.	Pregnancy related ADR	[AVE 010307]
	Pregnancy related ADR	[AVE 010309]
	Pregnancy related ADR	[AVE 010311]
	Pregnancy related ADR	[AVE 010314]
	Pregnancy related ADR	[AVE 010316]
	Pregnancy related ADR	[AVE 010318]
	Pregnancy related ADR	[AVE 010320]
	Pregnancy related ADR	[AVE 010322]
	Pregnancy related ADR	[AVE 010324]
	Pregnancy related ADR	[AVE 010326]
	Pregnancy related ADR	[AVE 010328]
	Pregnancy related ADR	[AVE 010331]
	{11:4,Q}	

11/3/2005 – 2/28/2006

49.	Pregnancy related ADR	[AVE 010334]
	Pregnancy related ADR	[AVE 010336]
	Pregnancy related ADR	[AVE 010338]
	Pregnancy related ADR	[AVE 010340]
	Pregnancy related ADR	[AVE 010342]
	Pregnancy related ADR	[AVE 010345]
	Pregnancy related ADR	[AVE 010347]
	Pregnancy related ADR	[AVE 010349]
	Pregnancy related ADR	[AVE 010351]
	Pregnancy related ADR	[AVE 010353]
	Pregnancy related ADR	[AVE 010356]
	Pregnancy related ADR	[AVE 010359]
	{11:4,R}	

3/1/2006 – 6/1/2006

50. Initial part of this book contains a request to the FDA for an exception on the submission of reports considered not to be serious.

Pregnancy related ADR	[AVE 010383]
Pregnancy related ADR	[AVE 010387]
Pregnancy related ADR	[AVE 010389]
Pregnancy related ADR	[AVE 010391]
Pregnancy related ADR	[AVE 010402]
Pregnancy related ADR	[AVE 010404]
Pregnancy related ADR	[AVE 010406]
Pregnancy related ADR	[AVE 010408]
Pregnancy related ADR	[AVE 010411]
{12:5,A}	

51.

Pregnancy related ADR	[AVE 010414]
Pregnancy related ADR	[AVE 010416]
Pregnancy related ADR	[AVE 010420]
Pregnancy related ADR	[AVE 010422]
Pregnancy related ADR	[AVE 010425]
Child related ADR	[AVE 010427]
Pregnancy related ADR	[AVE 010431]
{12:5,B}	

6/1/2006

52.

Pregnancy related ADR	[AVE 011950]
Pregnancy related ADR	[AVE 011952]
Pregnancy related ADR	[AVE 011954]
Pregnancy related ADR	[AVE 011956]
Pregnancy related ADR	[AVE 011958]
Pregnancy related ADR	[AVE 011960]
Pregnancy related ADR	[AVE 011962]
{12:5,C}	

6/5/2006 – 10/12/2006

53.

Pregnancy related ADR	[AVE 010434]
Pregnancy related ADR	[AVE 010440]
Pregnancy related ADR	[AVE 010442]
Pregnancy related ADR	[AVE 010446]
Pregnancy related ADR	[AVE 010448]

Pregnancy related ADR	[AVE 010450]
Pregnancy related ADR	[AVE 010453]
Pregnancy related ADR	[AVE 010455]
Pregnancy related ADR	[AVE 010459]
Pregnancy related ADR	[AVE 010462]
Pregnancy related ADR	[AVE 010467]
Pregnancy related ADR	[AVE 010474]
Pregnancy related ADR	[AVE 010476]
Pregnancy related ADR	[AVE 010479]
Pregnancy related ADR	[AVE 010481]
Pregnancy related ADR	[AVE 010485]
Pregnancy related ADR	[AVE 010487]
Pregnancy related ADR	[AVE 010489]
Pregnancy related ADR	[AVE 010491]
Pregnancy related ADR	[AVE 010493]
Pregnancy related ADR	[AVE 010495]
Pregnancy related ADR	[AVE 010498]
Pregnancy related ADR	[AVE 010500]

{12:5,D}

10/13/2006 – 1/31/2007

54. Pregnancy related ADRs
{12:5,E}

2/1/2007 – 5/31/2007

55. Pregnancy related ADRs
{12:5,F}

5/31/2007

56. Pregnancy related ADRs
{12:5,G}

6/4/2007 – 10/29/2007

57. Pregnancy related ADRs
{12:5,H}

11/5/2007 - Present

58. Pregnancy related ADRs
{12:5,I}

11/5/2007 – Present

59. Pregnancy related ADRs
{12:5,J}

[Internal] Contents

This tabulation is provided to facilitate identifying information that is to be distilled. The number to the left refers to the above listing of each group of referenced items, and the number to the right refers to the initial page # at which elaborative information exists.

As was done in the first letter, the above-cited binders were reviewed methodically; indeed, as this review is being initiated, knowledge of the contents of these files is not known to this reviewer, illustrating the "disinterested" approach that is being applied. Thus, each of these reports may be perceived as a "stand-alone" document, with the conclusions to be drawn following completion of this completed review unknown to the reviewer (this physician) at its initiation, on the date of this letter [11/13/2008]. Here, recognizing this is an unusual type of "certification" to be provided while generating an Expert Report, the goal is to mirror what Aventis "knew" before/after the Hill pregnancy.

1/2/2004 – 5/26/2004

41.	Pregnancy related ADR	[AVE 010179]
	Pregnancy related ADR	[AVE 010182]
	Fetal death ADR	[AVE 010184]
	Pregnancy related ADR	[AVE 010188]
	Litigation related ADR	[AVE 010190]
	Pregnancy related ADR	[AVE 010192]
	Pregnancy related ADR	[AVE 010194]
	Pregnancy related ADR	[AVE 010196]
	{MASTER BINDER 11:ADR 4, Section J}	

AVE 010179 depicts induced-abortion of a three-month old fetus (with hemorrhage, dwarfism, genitourinary anomalies) whose mother had a positive anticardiolipin; there was a retro-placental hemorrhage with chronic villous ischemia and small villosities.

AVE 010182 depicts a woman with *abruptio placentae*.

AVE 010184 depicts fetal death at 18-weeks' gestation following micro-emboli from a prosthetic valve.

AVE 010188 depicts fetal craniosynostosis with maternal Factor V deficiency.

AVE 010190 depicts a woman who developed *inter alia* a hematoma.

AVE 010192 depicts a woman who experienced premature birth at 29-weeks' gestation after spontaneous development of a placental hematoma with placental insufficiency; the woman was taking no other medication. "The physician considers the placental hematoma 'highly probably" related to Lovenox; in his opinion, a trauma is theoretically an alternative cause to explain the hematoma, but there was no evidence of a trauma."

Assessment: This case provides direct evidence of placental pathology from Lovenox.

AVE 010194 depicts fetal craniosynostosis with maternal Factor V deficiency.

AVE 010196 depicts multiple fetal anomalies with maternal Factor V deficiency.

5/27/2004 – 8/31/2004

42.	Pregnancy related ADR	[AVE 010199]
	Pregnancy related ADR	[AVE 010201]
	Fetal related ADR	[AVE 010203]
	Pregnancy related ADR	[AVE 010205]
	Pregnancy related ADR	[AVE 010207]
	Pregnancy related ADR	[AVE 010210]

Pregnancy related ADR	[AVE 010212]
Pregnancy related ADR	[AVE 010214]
Pregnancy related ADR	[AVE 010216]
Pregnancy related ADR	[AVE 010218]

{11:4,K}

AVE 010199 depicts premature rupture of membranes.

AVE 010201 depicts hydrocephaly and Dandy-Walker Syndrome in a fetus whose mother had ingested Coumadin.

AVE 010203 depicts development of a spontaneous placental hematoma at 20-weeks' gestation, yielding placental insufficiency and premature delivery at 29-weeks' gestation. "The physician considers the placental hematoma 'highly probably" related to Lovenox; in his opinion, a trauma is theoretically an alternative cause to explain the hematoma, but there was no evidence of a trauma."

Assessment: This hemorrhagic episode was undoubtedly due to Lovenox, but this case may actually recapitulate the "AVE 010192" case.

AVE 010205 depicts post-partum development of the HELLP Syndrome (hemolysis, elevated liver enzymes and thrombocytopenia).

AVE 010207 depicts hydrocephaly and Dandy-Walker syndrome, reciting AVE 010201.

AVE 010210 depicts a fetus with intestinal atresia.

AVE 010212 depicts a fetus with intestinal atresia, reciting AVE 010210.

AVE 010214 depicts the instant case.

AVE 010216 depicts spontaneous abortion, reciting AVE 010210 and AVE 010212.

AVE 010218 recites AVE 010210, AVE 010212, and AVE 010216.

9/1/2004 – 12/31/2004

43.	Pregnancy related ADR	[AVE 010221]
	Pregnancy related ADR	[AVE 010223]
	Pregnancy related ADR	[AVE 010226]
	Pregnancy related ADR	[AVE 010231]
	Pregnancy related ADR	[AVE 010234]
	Pregnancy related ADR	[AVE 010238]
	Pregnancy related ADR	[AVE 010242]
	Pregnancy related ADR	[AVE 010245]

Pregnancy related ADR [AVE 010250]
Pregnancy related ADR [AVE 010254]
{11:4,L}

AVE 010221 depicts spontaneous abortion and bruising.

Assessment: As was true with many submissions, the reporter did not check-off an assessment of the potential linkage of the drug with the sequella, nor did anyone else.

AVE 010223 depicts induced-birth of a stillborn fetus at 17-weeks' gestation; the case filing was accompanied by the following additional information (from returned syringes):

Addendum for follow up information received on 29-Nov-2004: Follow up information provided QA regarding enoxaparin sodium injection (Lovenox), PTC report 1000040301, lot #: 9467. The site has performed a batch record review on this batch. This batch was filled from the 10th to the 11th of March 2004, and was packaged from the 23rd to the 24th of March 2004. There are no deviations or other notations in the batch record that indicate any problem that might be related to the nature of this complaint. All chemical and microbiological controls performed prior to batchrelease met the specifications
Inspection of the returned samples: 66 samples were returned to Le Trait.
The following testswere performed by our Microbiology Quality Control Laboratory on the returned syringes:
-Anti Xa activity
-Anti IIa activity

All met the specifications. Inspection of retain samples at Le Trait :
The same tests were performed by our Microbiology QualityControl Laboratory on the retained syringes. All met the specifications
In-coming controls: All controls performed on raw materials (Enoxaparin, water and nitrogen) met the specifications.
Conclusion: As no defect was detected on the returned samples,this complaint is not considered as justified.
Finally, to answer the patient#s inquiry, the recommended temperature for storage is 25°C (77°F) with excursions permitted to 15#30°C (59#86°F).

Addendum for follow up information received on 08-Dec-2004: Follow up information provided QA regarding enoxaparin sodium injection (Lovenox), PTC report 1000040299, lot #: 9484. The site has performed a batch record review on this batch. This batch was filled from the 28th of May to the 1st of June 2004, and was packaged from the 14th to the 15th of June 2004. There are no deviations or other notations in the batch record that indicate any problem that might be related to the nature of this inspection of the returned samples
54 samples were returned to le Trait for investigation. The following tests were performed by our Microbiology Quality Control Laboratory on the returned syringes:
-Anti Xa activity
-Anti IIa activity

All met the specifications. Inspection of retain samples at Le Trait: The same tests were performed by our Microbiology Quality Control Laboratory on the retained syringes. All met the specification. In-coming controls: All controls performed on raw materials (Enoxaparin, water and nitrogen) met the specifications. Conclusion: As no defect was detected on the returned samples, this complaint is not considered as justified. Finally, to answer the patient#s inquiry, the recommended temperature for storage is 25°C (77°F) with excursions permitted to 15#30°C (59#86°F).

Assessment: Performance of this unprecedented level of detailed laboratory analysis raises the question as to why such detailed review was not directed at predecessor-cases.

AVE 010225 depicts congenital anomalies diagnosed a fortnight post-partum.

AVE 010231 depicts spontaneous abortion and bruising.

Assessment: As was true with many submissions, the reporter did not check-off an assessment of the potential linkage of the drug with the sequella, nor did anyone else. This appears to re-cite "AVE 010221."

AVE 010234 re-cites the "AVE 010223" case.

AVE 010237 re-cites the "AVE 010225" case.

Assessment: A cover-memo states that this information was conveyed [within "PH/US"] from Kim Bildstein to Lynne Agullar, John Rakshys and Jason Kraker (as well as to the BRW Document Center). It will be necessary to trace the content of the reviews by each of these people, as well as to compare/contrast the processing of this filing and others (such as those that are particularly problematic) through the BRW Document Center.

AVE 010242 depicts polyhydraminos and induced labor.

AVE 010245 depicts decreased amniotic fluid.

AVE 010250 re-cites the "AVE 010207" case.

AVE 010254 depicts spontaneous abortion at 10-weeks' gestation.

Assessment: As is the case with most every other report, review of the placenta is but one facet of the database that is not explored. Also, appended to the cover-memo is a set of attached documents, and it is vital to correlate same with other formal submissions.

1/3/2005 – 3/31/2005

44.	Pregnancy related ADR	[AVE 010257]
	Pregnancy related ADR	[AVE 010259]
	Pregnancy related ADR	[AVE 010261]
	Pregnancy related ADR	[AVE 010264]
	Pregnancy related ADR	[AVE 010266]
	Pregnancy related ADR	[AVE 010269]
	Pregnancy related ADR	[AVE 010271]
	{11:4,M}	

AVE 010257 depicts a fetal angioma.

AVE 010259 depicts a fetal ventricular septal defect.

AVE 010261 again depicts the instant case.

AVE 010264 depicts severe symptoms associated with contractions.

AVE 010266 depicts a newborn with dyspnea.

Assessment: Although no submitted-information suggested hemorrhage, it was sparse and unaccompanied by basic data regarding *inter alia* the status of the newborn.

AVE 010269 depicts total alopecia.

Assessment: Again, this was accompanied by a cover-memo from Kim Bildstein, R.Ph., who is Aventis' U.S. Reporting Officer responsible for "Global Pharmco-vigilance and Epidemiology" [spelled incorrectly on her e-mail], who is available at 908-231-2846. She appended a literature-article [200512294GDDC] which also needs to be reviewed.

AVE 010271 depicts a stillborn with blood clots in the cord which caused fetal-death at 36-weeks' gestation.

Assessment: This scenario is consistent with the potential for Lovenox to be implicated.

AVE 010274 depicts a pregnant woman who developed *inter alia* a bowel obstruction from an abdominal hematoma; it was felt to be "probably" associated with Lovenox.

Assessment: This scenario is consistent with the potential for Lovenox to be implicated, although the scenario is more related to what transpired maternally than fetally; this is another case in which further information is needed (particularly regarding the placenta).

45. Abstract: **Enoxaparin Treatment in 600 Pregnancies in Women with Pregnancy Loss and Thrombophilia** [Author: A. Sarto]
Source: JTH 2003; 1 Supplement 1 p.1898
[AVE 010277]

Pregnancy related ADR [AVE 010279]
Pregnancy related ADR [AVE 010281]
{11:4,N}

AVE 010279 [recapitulated as "AVE 010281"] depicts two premature infants born with DIC, and "Additional information is being requested."

Assessment: This is the proper response to receipt of such sparse information.

AVE 010277 depicts the abstract of a review article [plus an abbreviated citation thereof] derivative of data abstracted herein, as provided by Aventis [from 5/1996 – 5/2004].

Monitoring of "anti-Xa" levels (0.3 – 0.6 u/ml) occurred, with the Results as follows: "Gestational outcome of the treated pregnancies was compared with the outcome of previously untreated pregnancies in these women, in terms of pregnancy loss rate and late placental vascular complications rate. Statistical analysis in progress." The conclusion was definitive: "Preconceptional and gestational Lovenox adjusted in a fertility program is effective to prevent clinical and preclinical pregnancy losses in women with Recurrent Pregnancy Losses and Thrombophilia." Complications and Side-Effects were as follows: "DVT (one woman @ 34-weeks' gestation), total alopecia, and skin reactions (4 cases)."

The following is a tabular presentation of the gestational outcomes:

	Untreated Pregnancies	Treated pregnancies	p
N° of pregnancies	1541	600	
Pregnancy losses	1302 (84.5%)	97 (16%)	< 0.001
Preclinical	272 (17.5%)	10 (1.6%)	< 0.001
Embryonic	878 (57%)	80 (13.3%)*	< 0.001
Fetal	152 (10%)	7 (1.1%)**	< 0.001
Live births	239 (15.5%)	503 (84 %)	< 0.001
	2 twins	13 twins	
Intrauterine growth retardation	38 (15.9%)	14 (2.8%)	<0.05
Preeclampsia	32 (13.4%)	7 (1.4%)	<0.05
Congenital Malformations	Neural tube defect: 2 Cardiac malformations: 1	Cardiac malformations: 1 Duodenal atresia: 1	
Chromosomal syndromes	Down's syndrome: 1	Down's syndrome:2 Klinefelter's Syndrome: 1	

Assessment: Obviously, the entire article must be analyzed, as well as the interaction that occurred between the investigators and the Aventis personnel; for example, the decision to monitor anti-Xa (and to adjust dosages accordingly) is discordant with the claim that no such testing is needed. In addition, specific reference to placental pathology exists and, therefore, the supportive data must be probed and correlated with clinical bleeding (particularly in light of the information contained in the ADR files, as detailed herein). Also, the classification of the (seven) cases of pregnancy losses due to fetal anomalies must be examined because the abstracted information fail to identify prospectively the methodology to be employed when making such judgments. Also, the sum (five) of the subsequently-listed congenital malformations (cardiac and duodenal) and chromosomal syndromes (Down's and Klinefelter's) may or may not be related to the (14) cases of growth retardation; again, it is necessary to determine whether any were bleeding-related.

4/1/2005 – 5/26/2005

46. Pregnancy related ADR [AVE 010284]
Pregnancy related ADR [AVE 010286]
Pregnancy related ADR [AVE 010288]
Pregnancy related ADR [AVE 010291]
Pregnancy related ADR [AVE 010293]
Pregnancy related ADR [AVE 010295]

Duplicate copy of:
Abstract: **Enoxaparin Treatment in 600 Pregnancies in Women with Pregnancy Loss and Thrombophilia** [Author: A. Sarto]
Source: JTH 2003; 1 Supplement 1 p.1898
[AVE 010304]
{11:4,O}

AVE 010284 depicts spontaneous abortion due, possibly, to a congenital anomaly; further data had been requested, but none was contained with this follow-up report.

Assessment: It will be necessary to depict the tracking-system employed throughout, including how "ticklers" yielded cases in which requested information remained pending.

AVE 010288 depicts a baby with a low Apgar, acidosis, and grunting for 36 hours in a mother who had sustained a skin rash.

AVE 010291 depicts an abortion in a fetus with hemorrhage. No further information had been provided, and the case had not been substantiated by a health professional.

Assessment: Further information must be provided regarding this case for, obviously, there is a potential relationship between the instant case and the details thereof.

AVE 010293 depicts fetal demise at 27-weeks' gestation.

Assessment: Further information is needed to assess multiple concerns.

AVE 010295 depicts fetal demise and spontaneous abortion is a mother with *inter alia* hypothyroidism and hepatitis, viewed as HELLP Syndrome.

AVE 010297 depicts the Argentinean case of total alopecia (plus osteopenia) among the 600 cases that comprised the aforementioned article [contained again in this binder].

AVE 010301 depicts the 600-case review article; again, the complete text is omitted.

5/27/2005

47.	Pregnancy related ADR	[AVE 011943]
	Pregnancy related ADR	[AVE 011947]
	{11:4,P}	

AVE 011943 depicts a baby who subsequently developed hematochezia and hepatitis.

AVE 011947 depicts injection site bruising.

5/28/2005 – 10/28/2005

48.	Pregnancy related ADR	[AVE 010307]
	Pregnancy related ADR	[AVE 010309]
	Pregnancy related ADR	[AVE 010311]
	Pregnancy related ADR	[AVE 010314]
	Pregnancy related ADR	[AVE 010316]
	Pregnancy related ADR	[AVE 010318]
	Pregnancy related ADR	[AVE 010320]
	Pregnancy related ADR	[AVE 010322]
	Pregnancy related ADR	[AVE 010324]
	Pregnancy related ADR	[AVE 010326]
	Pregnancy related ADR	[AVE 010328]
	Pregnancy related ADR	[AVE 010331]
	{11:4,Q}	

AVE 010307 depicts spontaneous abortion (at 15-weeks' gestation) and excessive vaginal bleeding.

Assessment: It would be desirable to note (if nothing else) the status of the placenta.

AVE 010309 depicts maternal splenic rupture.

AVE 010311 depicts multiple fetal developmental anomalies.

AVE 010314 re-cites the "AVE 010309" case.

AVE 010316 depicts a "missed abortion" with "inconsistent information."

Assessment: More information should obviously have been requested regarding this case.

AVE 010318 depicts a fetus with a trigeminal angioma.

AVE 010320 depicts a woman who developed a retroplacental hematoma, prompting premature delivery of twins.

Assessment: Much more information is needed regarding this entire matter.

AVE 010322 re-cites the "AVE 010321" case.

AVE 010324 depicts a newborn with nystagmus and retinal anomalies.

AVE 010326 depicts fetal bradycardia.

Assessment: More data are needed regarding this case, to note any bleeding concern.

AVE 010328 depicts multiple congenital anomalies.

AVE 010331 depicts spontaneous abortion is a mother with a prosthetic heart valve.

11/3/2005 – 2/28/2006

49.	Pregnancy related ADR	[AVE 010334]
	Pregnancy related ADR	[AVE 010336]
	Pregnancy related ADR	[AVE 010338]
	Pregnancy related ADR	[AVE 010340]
	Pregnancy related ADR	[AVE 010342]
	Pregnancy related ADR	[AVE 010345]
	Pregnancy related ADR	[AVE 010347]
	Pregnancy related ADR	[AVE 010349]
	Pregnancy related ADR	[AVE 010351]
	Pregnancy related ADR	[AVE 010353]
	Pregnancy related ADR	[AVE 010356]
	Pregnancy related ADR	[AVE 010359]
	{11:4,R}	

AVE 010334 depicts spontaneous abortion associated with a placental hematoma.

Assessment: More information is needed regarding this case, for obvious reasons.

AVE 010336 depicts miscarriage of one fetus from a twin-gestation; it was associated with maternal hemorrhage.

Assessment: More information is needed regarding this case, with particular information needed regarding whether the other fetus developed any hemorrhage.

AVE 010338 depicts spontaneous abortion of a 7-weeks' gestation.

Assessment: As is true with all the spontaneous abortion cases, it is necessary to discern if any congenital anomalies existed, or whether they were associated with bleeding.

AVE 010340 depicts spontaneous abortion.

Assessment: More information is needed, for reasons aforementioned.

AVE 010342 depicts neonatal inter-ventricular communication.

AVE 010345 depicts missed abortion, which the reporting physician assumed was not related to the use of Lovenox.

Assessment: Again, more information is needed regarding this case, as well as why the reporting physician assumed there had been no impact of Lovenox.

AVE 010347 depicts spontaneous abortion and HELLP Syndrome.

Assessment: The reason for the spontaneous abortion must be determined.

AVE 010349 depicts a spontaneous abortion in an Argentinean patient.

Assessment: The details of this case would probably emerge following review of the cases that comprised the review article, although this will need to be confirmed.

AVE 010351 depicts spontaneous abortion and HELLP Syndrome in an Argentinean patient.

Assessment: Again, the details of this case must be assessed both independently and within the context of the 600-case review article.

AVE 010353 depicts neonatal subglottic stenosis and laryngomalacia associated with maternal hemorrhage at 11-weeks' gestation.

Assessment: Although Lovenox may not cause congenital malformations, it is possible that the hemorrhagic event was associated with this sequella.

AVE 010356 depicts miscarriage following placental hemorrhage and a fetal intracranial bleeding episode.

Assessment: Far more information is needed regarding the details of this case, for it is remarkably comparable to the instant case.

AVE 010359 re-cites the "AVE 010353" case.

3/1/2006 – 6/1/2006

50. Initial part of this book contains a request to the FDA for an exception on the submission of reports considered not to be serious.

Pregnancy related ADR	[AVE 010383]
Pregnancy related ADR	[AVE 010387]
Pregnancy related ADR	[AVE 010389]
Pregnancy related ADR	[AVE 010391]
Pregnancy related ADR	[AVE 010402]
Pregnancy related ADR	[AVE 010404]
Pregnancy related ADR	[AVE 010406]
Pregnancy related ADR	[AVE 010408]
Pregnancy related ADR	[AVE 010411]

{12:5,A}

AVE 010362 constitutes a 3/26/2006 letter to George Q. Mills, M.D. (Director of the Division of Medical Imaging and Hematology Products—HFD-160—in the FDA's Center for Drug Evaluation and Research) from Ms. Lynda Tetarenko (Manager of Aventis' US Affairs Marketed Products, @ 908-243-7377) that stated, in pertinent part [accompanied by submission of all relevant files on a CD-ROM (constituting 20 MB)]:

> Reference is made to letters dated June 21, 2005 in which, under 21 CFR §314.90, sanofi-aventis U.S. LLC, requested that the Agency waive the requirement to submit Periodic Adverse Drug Experience Reports (PADERs) in the format described in 21 CFR §314.80 and instead submit Periodic Safety Update Reports (PSURs), in the format described under ICH E2C guidance, for several Aventis products. Reference is also made to telephone conversations between Ms. Kathleen Frost of the Agency, Ms. Aparna Murthy and Ms. Lynda Tetarenko of sanofi-aventis on October 24, 2005 and December 12, 2005 addressing clarification questions asked by Aventis and recommendations made by the Agency.
> Reference is also made to a letter dated January 21, 2006, from the Agency, granting this request.
>
> **CERTIFICATION**
>
> I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:
>
> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
> 2. Biological establishment standards in 21 CFR Part 600.
> 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
> 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
> 5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
> 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
> 7. Local, state and Federal environmental impact laws.
>
> If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
> The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
> **Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

Assessment: This letter implies that Aventis was seeking confirmation that a lesser level of oversight was justified, notwithstanding the body of evidence accrued herein. It is, obviously, desirable to acquire all related correspondence, for the justification thereof must be compared/contrasted with the database. Essentially, despite not having pursued "leads" within the ADRs, Aventis sought the ability to gloss-over future submissions. Certainly, it will be vital to ensure that documentation is provided regarding the effort to "search existing data sources, gather and maintain the needed data, and review the data."

AVE 010369 depicts submission of "Not Serious" data.

Assessment: The justification for this assertion must be probed.

AVE 010370 depicts submission of a form averring "tolerance to drug."

Assessment: The justification for this assertion must be probed.

AVE 010372 depicts injection site irritation and hardening.

AVE 010374, AVE 010376 and AVE 010378 depict bleeding.

AVE 010381 depicts lack of drug effect.

AVE 010383, AVE 010385, AVE 010387, AVE 010389, AVE 010391, AVE 010393 and AVE 010395 depict the use of Lovenox during pregnancy.

AVE 010397 depicts pain at injection site.

AVE 010399 constitutes a cover-memo with two attachments.

Assessment: The contents of these attachments must be reviewed.

AVE 010400 depicts lack of drug effect, allegedly yielding a pulmonary embolism.

AVE 010402 depicts the development of autism in a baby.

AVE 010404 depicts the development of a placental clot plus decreased amniotic fluid; the former was characterized as "lack of drug effect" and the latter was characterized as "drug exposure via mother" which "shut down the placenta."

Assessment: This illustrates the potential for Lovenox to cause the paradoxical clotting [the hypothetical pathogenesis of which has been articulated *supra* and elsewhere].

AVE 010406 depicts a woman who developed a miscarriage.

Assessment: As has been the case elsewhere, more information is needed, here.

AVE 010408 depicts a woman who developed a miscarriage from placental thrombosis and whose newborn had an intracerebral bleed, allegedly due to a subarachnoid tear.

Assessment: It must be recognized both that this scenario mirrors concerns raised by the instant case and that the patients receiving Lovenox usually harbored a baseline level of hyperthrombosis that could be postulated to be the cause of placental thrombosis. Yet, the problem with the latter explanation is the otherwise efficacious use of Lovenox, particularly when associated with neonatal hemorrhage (as occurred in this case). Here, it is necessary to explore the reason why the possibility of an "arachnoid tear" was raised.

AVE 010411 depicts miscarriage of one twin, associated with hemorrhage.

Assessment: Again, it is desirable to examine the circumstances related to this event including, in particular, the effect on the unaffected (at that time) fetus.

51.	Pregnancy related ADR	[AVE 010414]
	Pregnancy related ADR	[AVE 010416]
	Pregnancy related ADR	[AVE 010420]
	Pregnancy related ADR	[AVE 010422]
	Pregnancy related ADR	[AVE 010425]
	Child related ADR	[AVE 010427]
	Pregnancy related ADR	[AVE 010431]
	{12:5,B}	

AVE 010414 depicts a woman who developed symptoms and signs of pre-eclampsia (hypertension, azotemia and proteinuria) who delivered a daughter who died from hemorrhage that was initially intra-cerebral and subsequently intra-pulmonary.

Assessment: Again, more information is needed to explain why the baby bled.

AVE 010416 depicts a baby who demonstrated autism at age 16-months.

AVE 010420 re-cites the "AVE 010404" case.

AVE 010422 depicts neonatal pulmonary hypertension associated with placental chorio-amnionitis; other pre-natal drug exposures included amoxicillin, nifedipine, atosiban, and beta-methasone.

Assessment: Although there was no hemorrhagic component to this case-narrative, noting that the placental pathology had been provided spontaneously illustrates how simple it would have been to have requested this information routinely in these cases.

AVE 010425 depicts neonatal intracerebral (subaponeurotic/subarachnoid) hemorrhage for which fresh-frozen-plasma transfusion was successful; Lovenox had been given 8 (eight) hours pre-delivery by Caesarian section (due to prolongation of the second stage of labor due to malposition associated with a bulging fontanelle, following failure of manual rotation). The daughter had Apgar scores of 8/9 and survived.

Assessment: Although this case is from Malaysia, if there was sufficient wherewithal to have generated a report, there was sufficient justification to anticipate that a request for further information would have been honored. Indeed, more information was provided from this site than had been provided by upwards of 95% of the American/British/French.

AVE 010427 depicts a newborn with sensory integration dysfunction, head bobbing, tactile defensiveness, and central hypotonia ("sitting in the air").

AVE 101430 depicts a memo from Tatyana Lomax to the BRW Document Center.

Assessment: Again, knowledge of the attachments is desirable.

AVE 010431 re-cites the "AVEs 010414" case.

6/1/2006

52.	Pregnancy related ADR	[AVE 011950]
	Pregnancy related ADR	[AVE 011952]
	Pregnancy related ADR	[AVE 011954]
	Pregnancy related ADR	[AVE 011956]
	Pregnancy related ADR	[AVE 011958]
	Pregnancy related ADR	[AVE 011960]
	Pregnancy related ADR	[AVE 011962]
	{12:5,C}	

AVE 011950 depicts a pregnant woman with an enhanced hemorrhagic tendency (epistaxis, hematuria, diffuse).

AVE 011952 depicts a pregnant woman with enhanced vaginal bleeding.

AVE 011954 depicts a pregnant woman with spotting.

AVE 011956 depicts a pregnant woman with *inter alia* injection-site bleeding.

AVE 011958 depicts a pregnant woman with hematochezia.

AVE 011960 depicts a pregnant woman with hematomas and easy bruisability.

AVE 011962 depicts a pregnant woman with injection-site bleeding.

6/5/2006 – 10/12/2006

53.	Pregnancy related ADR	[AVE 010434]
	Pregnancy related ADR	[AVE 010440]
	Pregnancy related ADR	[AVE 010442]
	Pregnancy related ADR	[AVE 010446]
	Pregnancy related ADR	[AVE 010448]
	Pregnancy related ADR	[AVE 010450]
	Pregnancy related ADR	[AVE 010453]
	Pregnancy related ADR	[AVE 010455]
	Pregnancy related ADR	[AVE 010459]
	Pregnancy related ADR	[AVE 010462]
	Pregnancy related ADR	[AVE 010467]
	Pregnancy related ADR	[AVE 010474]
	Pregnancy related ADR	[AVE 010476]
	Pregnancy related ADR	[AVE 010479]
	Pregnancy related ADR	[AVE 010481]
	Pregnancy related ADR	[AVE 010485]
	Pregnancy related ADR	[AVE 010487]
	Pregnancy related ADR	[AVE 010489]
	Pregnancy related ADR	[AVE 010491]
	Pregnancy related ADR	[AVE 010493]
	Pregnancy related ADR	[AVE 010495]
	Pregnancy related ADR	[AVE 010498]
	Pregnancy related ADR	[AVE 010500]
	{12:5,D}	

AVE 010434 depicts a pregnant woman with uteroplacental insufficiency, umbilical vein thrombosis, thrombi in surface chorionic veins, placental infarction, vascular obliteration with stem vessel thrombosis, obliterative changes in fetal vessels and areas of villous stromal fibrosis, possible acute vasculitis of the umbilical cord, and chorioamnionitis. Along with (not unanticipated) leukocytosis, there was abnormal RBC-morphology.

Blood samples were sent to Wisconsin for two reasons; first, to detect HIT and, second, to determine if the mother had antibodies that agglutinated with the father's blood. Unknown are the results of this test and the status of the offspring. Administratively, this case was referred via the Legal Department, and an error in the numbering system (case manufacturer number) was detected and corrected (for unexplained reasons).

Assessment: The extensive report of placental pathology again contrasts dramatically with the dearth of comparable data in other patients. Follow-up information regarding the status of the offspring and the results of parental tests are pending and, again, logistical decision-making regarding the rationale for these studies contrasts with the absence of comparable (indeed, "any") such evaluations in most every other case, here. And the pathway from the Legal Department contrasts with other cases, inexplicably, raising questions as to how the case entered the system in this fashion, in the first place.

AVE 010442 depicts the instant case.

AVE 010446 depicts neonatal hypospadias.

AVE 010448 depicts a first-trimester miscarriage.

AVE 010450 depicts the instant case; in the narrative, "shaken baby syndrome" was raised and denied by the parents.

AVE 010453 depicts intrauterine death associated with Trisomy 21.

AVE 010455 re-cites the "AVE 010434" case.

AVE 010459 depicts congenital patent foramen ovale.

AVE 010462 re-cites the "AVE 010411" case.

AVE 010465 depicts a man who died from a hemorrhagic stroke.

AVE 010467 depicts the instant case.

AVE 010470 depicts asymptomatic post-partum neutropenia.

AVE 010474 re-cites the prior "AVE 010411/AVE 010462" case.

AVE 010476 depicts the instant case.

Assessment: It has been assumed that every relevant case was "flagged" by the individual who prepared the binders. Therefore, because of the paucity of "case recitation" cases, it appears that few cases constituted the provision of "addenda" with further information.

AVE 010479 depicts transient pyrogenic shock in a pregnant woman.

AVE 010481 re-cites the prior "AVE/010411/AVE/010462/AVE 010472" case.

AVE 010485 depicts a woman who developed tachycardia, nausea and asthenia.

AVE 010487 depicts a woman who experienced a first-trimester spontaneous abortion.

AVE 010489 depicts the instant case.

AVE 010491 depicts a woman who underwent an elective first-trimester abortion.

AVE 010493 depicts neonatal craniosynostosis and subsequent autism.

AVE 010495 depicts neonatal club feet and shortening of Achilles tendon.

AVE 010498 depicts neonatal decrease in amniotic fluid.

AVE 010500 depicts a woman who experienced a spontaneous first-trimester abortion.

10/13/2006 – 1/31/2007

54. Pregnancy related ADRs
{12:5,E}

AVE 010503 depicts premature delivery of a neonate with growth retardation.

AVE 010505 depicts a woman who experienced a spontaneous abortion.

AVE 010508 depicts a woman who experienced a spontaneous abortion.

AVE 010510 depicts the instant case.

AVE 010514 depicts a "non-serious" case of *inter alia* intrauterine death.

Assessment: It is necessary to determine how cases were deigned to be "serious" or "non-serious."

AVE 010516 depicts a neonatal adjustment disturbance.

AVE 010518 depicts the instant case.

AVE 010526 depicts the instant case and contains the names of the involved individuals (on page AVE 010529).

Assessment: The reason for violation of confidentiality concerns must be established.

AVE 010540 re-cites the prior "AVE/010411/AVE/010462/AVE 010472/AVE 010481" case.

AVE 010546 re-cites the "AVE 010514" case, again without explaining why it was termed "non-serious."

AVE 010548 depicts the instant case.

AVE 010558 depicts massive subchorionic hematoma following Lovenox at a dosage of 80 mg BID, published in *Obstetrics and Gynecology* [108(3)(Part 2):707-709 (2006)].

The entire text of its portrayal is as follows:

> A 30 year-old pregnant female developed a massive hematoma while receiving Lovenox to prevent thrombosis. The patient's medical history included atrial fibrillation, a mitral valve replacement in 1990 performed in Mexico, and a bioprosthetic heart valve. Concomitant medications included oral digoxin 0.25 mg daily, warfarin and unfractionated Heparin 5000 international units daily.
>
> At approximately 5-weeks' gestation, the woman's anticoagulation was changed from unfractionated Heparin to subcutaneous Lovenox (60 mg BID). At 17-weeks' gestation, the Lovenox dose was increased to 70 mg BID to maintain a trough anti-Xa level of 0.5 units/ml or higher. At 19-weeks' gestation, a submembranous hematoma that was 13 x 12 x 15 cm^3 in size was detected and the patient revealed that she had been taking 80 mg of Lovenox BID instead of her prescribed dosage. At the time, her hemoglobin level was 7.8 g/dl.
>
> The patient's Lovenox dosage was subsequently reduced to 60 mg BID, then reduced further to 40 mg BID at 21-weeks' gestation. The hematoma and fetus were evaluated weekly. The hematoma increased to a maximum size of 20 x 20 x 17 cm^3, but the fetus continued to demonstrate adequate growth. The woman's Lovenox dosage was increased again to 50 mg BID. At 35-weeks' gestation, she presented with preterm premature rupture of membranes and preterm labor. A neonate girl with Apgar scores of 5, 6, 7 was delivered by a Caesarian section.
>
> Approximately 1 liter of brown fluid was gushed from the uterine incision before amniotomy and the total estimated blood loss was 600 m.. The placental pathology did not reveal any signs of abruption and was otherwise unremarkable. The woman was discharged on postpartum day 5 in stable condition, receiving warfarin for anticoagulation, metoprolol, digoxin and furosemide. The neonate was admitted to the intensive care unit for prematurity and respiratory depression associated with general anesthesia; she was discharged in good condition 10 days after birth.

Assessment: This article needs to be scrutinized, and the effect upon Aventis gauged; although the patient had a prosthetic valve, how the hemorrhage (and hemorrhagic risk, noting the acquisition of anti-Xa) was managed (and portrayed in the published piece) will reflect how characteristics of this case were (or were not) transformed into action.

AVE 010562 depicts the instant case.

Assessment: It will be necessary to compare/contrast these recapitulations of one case, inasmuch as it is unclear why it is repetitively filed.

AVE 010570 depicts tubal rupture of an ectopic pregnancy.

2/1/2007 – 5/31/2007

55. Pregnancy related ADRs
{12:5,F}

AVE 010573 depicts a woman who experienced a spontaneous abortion.

AVE 010575 depicts a woman who underwent a second-trimester elective abortion after an MRI revealed that the fetus had hydrocephaly and bi-ventricular dilatation.

AVE 010577 depicts the instant case.

AVE 010581 re-cites the prior "AVE/010411/AVE/010462/AVE 010472/AVE 010481/ AVE 010540" case.

AVE 010588 depicts the instant case.

AVE 010592 re-cites the prior "AVE/010411/AVE/010462/AVE 010472/AVE 010481/ AVE 010540/AVE 010581" case.

AVE 010599 depicts seven patients (with acute myocardial infarctions, per ST-elevation on EKG) who died after they had received off-label use of Lovenox over a period of seven months; six died from intracerebral hemorrhages and one from a GI-bleed. Follow-up information was received after the hospital nurse had been contacted; also, the hospital received coroner's reports regarding two of the (six) patients who had died from "strokes," and it was noted that this had been "caused by drug treatment."

Assessment: Although it was admirable (and rare) that the hospital nurse had been called, the supplied information remained woefully incomplete; if informed of the possible etiology of two patients' demises were from a "therapeutic misadventure," it is even more necessary to probe the details of what had transpired (drug dosages, monitoring, etc.)

AVE 010601 re-cites the prior "AVE/010411/AVE/010462/AVE 010472/AVE 010481/ AVE 010540/AVE 010581/AVE 010592" case.

AVE 010808 depicts the instant case.

AVE 010814 depicts a woman who experienced a spontaneous abortion. Concomitant medications and medical history were not initially provided; subsequently, the case was upgraded to "serious" and it was noted she had diabetes and took "a lot of medication." Lot and expiration date was not provided. Additional information was not provided.

Assessment: Despite specification of continually missing data, they weren't acquired.

AVE 010817 depicts a woman who experienced a post-partum cerebral hemorrhage; she had had a history of heart surgery, and the newborn had had growth retardation.

AVE 010819 depicts a woman who experienced a spontaneous first-trimester abortion; prior amniocentesis and weekly ultrasounds had been normal.

AVE 010821 depicts a patient/physician who reported she experienced no effect from Lovenox (documented by anti-Xa determinations) and subsequent thrombotic events. [Extensive detail is provided, including her rationale for drawing medical decisions.]

Assessment: This educated patient could adjudge her medical course invoking a lab test; similarly, such energies could/should have been expended following myriad other cases.

AVE 010825 depicts the instant case.

5/31/2007

56. Pregnancy related ADRs
{12:5,G}

AVE 010865 depicts cerebral palsy in the offspring of a woman who had used Lovenox.

AVE 010867 depicts a patient who had bruising at the site of injections.

AVE 010874 depicts a pregnant woman who ingested Lovenox without complication.

AVE 01076 depicts a patient who had bruising at the site of injections.

6/4/2007 – 10/29/2007

57. Pregnancy related ADRs
{12:5,H}

AVE 010636 depicts a woman who experienced a spontaneous abortion.

AVE 010638 depicts a woman who experienced a spontaneous second-trimester abortion.

AVE 010641 depicts a woman who experienced a spontaneous first-trimester abortion.

AVE 010643 depicts a woman who experienced premature labor.

AVE 010646 depicts a woman who fainted after she received a Lovenox injection.

AVE 010648 depicts a patient who developed HIT.

11/5/2007 - Present

58. Pregnancy related ADRs
{12:5,I}

AVE 010654 re-cites the prior "AVE/010411/AVE/010462/AVE 010472/AVE 010481/ AVE 010540/AVE 010581/AVE 010592" case.

11/5/2007 – Present

59. Pregnancy related ADRs
{12:5,J}

AVE 011979 depicts a woman who experienced a spontaneous abortion.

AVE 011981 depicts a woman who experienced a spontaneous abortion.

AVE 011984 depicts a neonate who developed hemorrhage (cardiac and post-LP).

AVE 011988 depicts a woman who experienced a spontaneous abortion.

AVE 011990 depicts a woman who experienced a spontaneous abortion.

AVE 011998 re-cites the prior "AVE/010411/AVE/010462/AVE 010472/AVE 010481/ AVE 010540/AVE 010581/AVE 010592/AVE 010654" case.

AVE 011999 depicts a woman who experienced premature labor.

AVE 012001 depicts a newborn with a hypoplastic left heart.

AVE 012003 depicts a pregnant woman who developed a rash.

AVE 012005 depicts a therapeutic abortion of a fetus with spina bifida.

AVE 012007 re-cites the prior "AVE/010411/AVE/010462/AVE 010472/AVE 010481/ AVE 010540/AVE 010581/AVE 010592/AVE 010654/AVE 011998" case.

AVE 012014 depicts the instant case.

AVE 012024 depicts a woman who experienced spontaneous first-trimester abortion.

AVE 012026 re-cites the prior "AVE/010411/AVE/010462/AVE 010472/AVE 010481/ AVE 010540/AVE 010581/AVE 010592/AVE 010654/AVE 011998/AVE 012007" case.

Distillations

AVE 010192 depicts a woman who experienced premature birth at 29-weeks' gestation after spontaneous development of a placental hematoma with placental insufficiency; the woman was taking no other medication. "The physician considers the placental hematoma 'highly probably" related to Lovenox; in his opinion, a trauma is theoretically an alternative cause to explain the hematoma, but there was no evidence of a trauma."

Assessment: This case provides direct evidence of placental pathology from Lovenox.

AVE 010203 depicts development of a spontaneous placental hematoma at 20-weeks' gestation, yielding placental insufficiency and premature delivery at 29-weeks' gestation. "The physician considers the placental hematoma 'highly probably" related to Lovenox; in his opinion, a trauma is theoretically an alternative cause to explain the hematoma, but there was no evidence of a trauma."

Assessment: This hemorrhagic episode was undoubtedly due to Lovenox, but this case may actually recapitulate the "AVE 010192" case.

AVE 010221 depicts spontaneous abortion and bruising.

Assessment: As was true with many submissions, the reporter did not check-off an assessment of the potential linkage of the drug with the sequella, nor did anyone else.

AVE 010223 depicts induced-birth of a stillborn fetus at 17-weeks' gestation; the case filing was accompanied by the following additional information (from returned syringes):

[indent deleted]

Assessment: Performance of this unprecedented level of detailed laboratory analysis raises the question as to why such detailed review was not directed at predecessor-cases.

AVE 010231 depicts spontaneous abortion and bruising.

Assessment: As was true with many submissions, the reporter did not check-off an assessment of the potential linkage of the drug with the sequella, nor did anyone else. This appears to re-cite "AVE 010221."

AVE 010237 re-cites the "AVE 010225" case.

Assessment: A cover-memo states that this information was conveyed [within "PH/US"] from Kim Bildstein to Lynne Agullar, John Rakshys and Jason Kraker (as well as to the BRW Document Center). It will be necessary to trace the content of the reviews by each of these people, as well as to compare/contrast the processing of this filing and others (such as those that are particularly problematic) through the BRW Document Center.

AVE 010254 depicts spontaneous abortion at 10-weeks' gestation.

Assessment: As is the case with most every other report, review of the placenta is but one facet of the database that is not explored. Also, appended to the cover-memo is a set of attached documents, and it is vital to correlate same with other formal submissions.

AVE 010266 depicts a newborn with dyspnea.

Assessment: Although no submitted-information suggested hemorrhage, it was sparse and unaccompanied by basic data regarding *inter alia* the status of the newborn.

AVE 010269 depicts total alopecia.

Assessment: Again, this was accompanied by a cover-memo from Kim Bildstein, R.Ph., who is Aventis' U.S. Reporting Officer responsible for "Global Pharmco-vigilance and Epidemiology" [spelled incorrectly on her e-mail], who is available at 908-231-2846. She appended a literature-article [200512294GDDC] which also needs to be reviewed.

AVE 010271 depicts a stillborn with blood clots in the cord which caused fetal-death at 36-weeks' gestation.

Assessment: This scenario is consistent with the potential for Lovenox to be implicated.

AVE 010274 depicts a pregnant woman who developed *inter alia* a bowel obstruction from an abdominal hematoma; it was felt to be "probably" associated with Lovenox.

Assessment: This scenario is consistent with the potential for Lovenox to be implicated, although the scenario is more related to what transpired maternally than fetally; this is another case in which further information is needed (particularly regarding the placenta).

AVE 010279 [recapitulated as "AVE 010281"] depicts two premature infants born with DIC, and "Additional information is being requested."

Assessment: This is the proper response to receipt of such sparse information.

AVE 010277 depicts the abstract of a review article [plus an abbreviated citation thereof] derivative of data abstracted herein, as provided by Aventis [from 5/1996 – 5/2004].

Monitoring of "anti-Xa" levels (0.3 – 0.6 u/ml) occurred, with the Results as follows: "Gestational outcome of the treated pregnancies was compared with the outcome of previously untreated pregnancies in these women, in terms of pregnancy loss rate and late placental vascular complications rate. Statistical analysis in progress." The conclusion was definitive: "Preconceptional and gestational Lovenox adjusted in a fertility program is effective to prevent clinical and preclinical pregnancy losses in women with Recurrent Pregnancy Losses and Thrombophilia." Complications and Side-Effects were as follows: "DVT (one woman @ 34-weeks' gestation), total alopecia, and skin reactions (4 cases)."

The following is a tabular presentation of the gestational outcomes:

[insert deleted]

Assessment: Obviously, the entire article must be analyzed, as well as the interaction that occurred between the investigators and the Aventis personnel; for example, the decision to monitor anti-Xa (and to adjust dosages accordingly) is discordant with the claim that no such testing is needed. In addition, specific reference to placental pathology exists and, therefore, the supportive data must be probed and correlated with clinical bleeding (particularly in light of the information contained in the ADR files, as detailed herein). Also, the classification of the (seven) cases of pregnancy losses due to fetal anomalies must be examined because the abstracted information fail to identify prospectively the methodology to be employed when making such judgments. Also, the sum (five) of the subsequently-listed congenital malformations (cardiac and duodenal) and chromosomal syndromes (Down's and Klinefelter's) may or may not be related to the (14) cases of growth retardation; again, it is necessary to determine whether any were bleeding-related.

AVE 010284 depicts spontaneous abortion due, possibly, to a congenital anomaly; further data had been requested, but none was contained with this follow-up report.

Assessment: It will be necessary to depict the tracking-system employed throughout, including how "ticklers" yielded cases in which requested information remained pending.

AVE 010291 depicts an abortion in a fetus with hemorrhage. No further information had been provided, and the case had not been substantiated by a health professional.

Assessment: Further information must be provided regarding this case for, obviously, there is a potential relationship between the instant case and the details thereof.

AVE 010293 depicts fetal demise at 27-weeks' gestation.

Assessment: Further information is needed to assess multiple concerns.

AVE 010307 depicts spontaneous abortion (at 15-weeks' gestation) and excessive vaginal bleeding.

Assessment: It would be desirable to note (if nothing else) the status of the placenta.

AVE 010316 depicts a "missed abortion" with "inconsistent information."

Assessment: More information should obviously have been requested regarding this case.

AVE 010320 depicts a woman who developed a retroplacental hematoma, prompting premature delivery of twins.

Assessment: Much more information is needed regarding this entire matter.

AVE 010326 depicts fetal bradycardia.

Assessment: More data are needed regarding this case, to note any bleeding concern.

AVE 010334 depicts spontaneous abortion associated with a placental hematoma.

Assessment: More information is needed regarding this case, for obvious reasons.

AVE 010336 depicts miscarriage of one fetus from a twin-gestation; it was associated with maternal hemorrhage.

Assessment: More information is needed regarding this case, with particular information needed regarding whether the other fetus developed any hemorrhage.

AVE 010338 depicts spontaneous abortion of a 7-weeks' gestation.

Assessment: As is true with all the spontaneous abortion cases, it is necessary to discern if any congenital anomalies existed, or whether they were associated with bleeding.

AVE 010340 depicts spontaneous abortion.

Assessment: More information is needed, for reasons aforementioned.

AVE 010345 depicts missed abortion, which the reporting physician assumed was not related to the use of Lovenox.

Assessment: Again, more information is needed regarding this case, as well as why the reporting physician assumed there had been no impact of Lovenox.

AVE 010347 depicts spontaneous abortion and HELLP Syndrome.

Assessment: The reason for the spontaneous abortion must be determined.

AVE 010349 depicts a spontaneous abortion in an Argentinean patient.

Assessment: The details of this case would probably emerge following review of the cases that comprised the review article, although this will need to be confirmed.

AVE 010351 depicts spontaneous abortion and HELLP Syndrome in an Argentinean patient.

Assessment: Again, the details of this case must be assessed both independently and within the context of the 600-case review article.

AVE 010353 depicts neonatal subglottic stenosis and laryngomalacia associated with maternal hemorrhage at 11-weeks' gestation.

Assessment: Although Lovenox may not cause congenital malformations, it is possible that the hemorrhagic event was associated with this sequella.

AVE 010356 depicts miscarriage following placental hemorrhage and a fetal intracranial bleeding episode.

Assessment: Far more information is needed regarding the details of this case, for it is remarkably comparable to the instant case.

AVE 010362 constitutes a 3/26/2006 letter to George Q. Mills, M.D. (Director of the Division of Medical Imaging and Hematology Products—HFD-160—in the FDA's Center for Drug Evaluation and Research) from Ms. Lynda Tetarenko (Manager of Aventis' US Affairs Marketed Products, @ 908-243-7377) that stated, in pertinent part [accompanied by submission of all relevant files on a CD-ROM (constituting 20 MB)]….

Assessment: This letter implies that Aventis was seeking confirmation that a lesser level of oversight was justified, notwithstanding the body of evidence accrued herein. It is, obviously, desirable to acquire all related correspondence, for the justification thereof must be compared/contrasted with the database. Essentially, despite not having pursued "leads" within the ADRs, Aventis sought the ability to gloss-over future submissions. Certainly, it will be vital to ensure that documentation is provided regarding the effort to "search existing data sources, gather and maintain the needed data, and review the data."

AVE 010369 depicts submission of "Not Serious" data.

Assessment: The justification for this assertion must be probed.

AVE 010370 depicts submission of a form averring "tolerance to drug."

Assessment: The justification for this assertion must be probed.

AVE 010399 constitutes a cover-memo with two attachments.

Assessment: The contents of these attachments must be reviewed.

AVE 010404 depicts the development of a placental clot plus decreased amniotic fluid; the former was characterized as "lack of drug effect" and the latter was characterized as "drug exposure via mother" which "shut down the placenta."

Assessment: This illustrates the potential for Lovenox to cause the paradoxical clotting [the hypothetical pathogenesis of which has been articulated *supra* and elsewhere].

AVE 010406 depicts a woman who developed a miscarriage.

Assessment: As has been the case elsewhere, more information is needed, here.

AVE 010408 depicts a woman who developed a miscarriage from placental thrombosis and whose newborn had an intracerebral bleed, allegedly due to a subarachnoid tear.

Assessment: It must be recognized both that this scenario mirrors concerns raised by the instant case and that the patients receiving Lovenox usually harbored a baseline level of hyperthrombosis that could be postulated to be the cause of placental thrombosis. Yet, the problem with the latter explanation is the otherwise efficacious use of Lovenox, particularly when associated with neonatal hemorrhage (as occurred in this case). Here, it is necessary to explore the reason why the possibility of an "arachnoid tear" was raised.

AVE 010411 depicts miscarriage of one twin, associated with hemorrhage.

Assessment: Again, it is desirable to examine the circumstances related to this event including, in particular, the effect on the unaffected (at that time) fetus.

AVE 010414 depicts a woman who developed symptoms and signs of pre-eclampsia (hypertension, azotemia and proteinuria) who delivered a daughter who died from hemorrhage that was initially intra-cerebral and subsequently intra-pulmonary.

Assessment: Again, more information is needed to explain why the baby bled.

AVE 010422 depicts neonatal pulmonary hypertension associated with placental chorio-amnionitis; other pre-natal drug exposures included amoxicillin, nifedipine, atosiban, and beta-methasone.

Assessment: Although there was no hemorrhagic component to this case-narrative, noting that the placental pathology had been provided spontaneously illustrates how simple it would have been to have requested this information routinely in these cases.

AVE 010425 depicts neonatal intracerebral (subaponeurotic/subarachnoid) hemorrhage for which fresh-frozen-plasma transfusion was successful; Lovenox had been given 8 (eight) hours pre-delivery by Caesarian section (due to prolongation of the second stage of labor due to malposition associated with a bulging fontanelle, following failure of manual rotation). The daughter had Apgar scores of 8/9 and survived.

Assessment: Although this case is from Malaysia, if there was sufficient wherewithal to have generated a report, there was sufficient justification to anticipate that a request for further information would have been honored. Indeed, more information was provided from this site than had been provided by upwards of 95% of the American/British/French.

AVE 101430 depicts a memo from Tatyana Lomax to the BRW Document Center.

Assessment: Again, knowledge of the attachments is desirable.

AVE 010434 depicts a pregnant woman with uteroplacental insufficiency, umbilical vein thrombosis, thrombi in surface chorionic veins, placental infarction, vascular obliteration with stem vessel thrombosis, obliterative changes in fetal vessels and areas of villous stromal fibrosis, possible acute vasculitis of the umbilical cord, and chorioamnionitis. Along with (not unanticipated) leukocytosis, there was abnormal RBC-morphology.

Blood samples were sent to Wisconsin for two reasons; first, to detect HIT and, second, to determine if the mother had antibodies that agglutinated with the father's blood. Unknown are the results of this test and the status of the offspring. Administratively, this case was referred via the Legal Department, and an error in the numbering system (case manufacturer number) was detected and corrected (for unexplained reasons).

Assessment: The extensive report of placental pathology again contrasts dramatically with the dearth of comparable data in other patients. Follow-up information regarding the status of the offspring and the results of parental tests are pending and, again, logistical decision-making regarding the rationale for these studies contrasts with the absence of comparable (indeed, "any") such evaluations in most every other case, here. And the pathway from the Legal Department contrasts with other cases, inexplicably, raising questions as to how the case entered the system in this fashion, in the first place.

AVE 010476 depicts the instant case.

Assessment: It has been assumed that every relevant case was "flagged" by the individual who prepared the binders. Therefore, because of the paucity of "case recitation" cases, it appears that few cases constituted the provision of "addenda" with further information.

AVE 010514 depicts a "non-serious" case of *inter alia* intrauterine death.

Assessment: It is necessary to determine how cases were deigned to be "serious" or "non-serious."

AVE 010526 depicts the instant case and contains the names of the involved individuals (on page AVE 010529).

Assessment: The reason for violation of confidentiality concerns must be established.

AVE 010558 depicts massive subchorionic hematoma following Lovenox at a dosage of 80 mg BID, published in *Obstetrics and Gynecology* [108(3)(Part 2):707-709 (2006)]….

Assessment: This article needs to be scrutinized, and the effect upon Aventis gauged; although the patient had a prosthetic valve, how the hemorrhage (and hemorrhagic risk, noting the acquisition of anti-Xa) was managed (and portrayed in the published piece) will reflect how characteristics of this case were (or were not) transformed into action.

AVE 010562 depicts the instant case.

Assessment: It will be necessary to compare/contrast these recapitulations of one case, inasmuch as it is unclear why it is repetitively filed.

AVE 010599 depicts seven patients (with acute myocardial infarctions, per ST-elevation on EKG) who died after they had received off-label use of Lovenox over a period of seven months; six died from intracerebral hemorrhages and one from a GI-bleed. Follow-up information was received after the hospital nurse had been contacted; also, the hospital received coroner's reports regarding two of the (six) patients who had died from "strokes," and it was noted that this had been "caused by drug treatment."

Assessment: Although it was admirable (and rare) that the hospital nurse had been called, the supplied information remained woefully incomplete; if informed of the possible etiology of two patients' demises were from a "therapeutic misadventure," it is even more necessary to probe the details of what had transpired (drug dosages, monitoring, etc.)

AVE 010814 depicts a woman who experienced a spontaneous abortion. Concomitant medications and medical history were not initially provided; subsequently, the case was upgraded to "serious" and it was noted she had diabetes and took "a lot of medication." Lot and expiration date was not provided. Additional information was not provided.

Assessment: Despite specification of continually missing data, they weren't acquired.

AVE 010821 depicts a patient/physician who reported she experienced no effect from Lovenox (documented by anti-Xa determinations) and subsequent thrombotic events. [Extensive detail is provided, including her rationale for drawing medical decisions.]

Assessment: This educated patient could adjudge her medical course invoking a lab test; similarly, such energies could/should have been expended following myriad other cases.

Distillation of Distillations

Thematic herein as been the dyad of problematic data and the lack of follow-up thereof. The former conclusion was confirmed when numerous cases related to neonatal bleeding were identified, and the latter conclusion was confirmed when numerous cases of issues that could be problematic were not pursued. Indeed, regarding the former, when the concept of transplacental passage could be entertained, cases were amazingly on-point relative to the instant case; indeed, regarding the latter, when the capacity to request such follow-up had been demonstrated elsewhere, the absence of inquiry was glaring.

The mistaken impression could be drawn that a generic level of concern was created when those responsible for oversight (FDA/Aventis) did not show evidence of doing so; rather, it was the specific focus on such documented concerns as placental pathology [*see* **AVE 010192**] that animates this concern. The same is true with anti-Xa testing [*see* **AVE 010223**] and myriad cases of abortion/miscarriage/premature-labor.

That those who submitted the forms never checked-off the initial impressions drawn is another area of concern. Tracing how these issues were addressed internally by Aventis will necessarily trace how internal memos were translated into policy [*see* **AVE 010237**] by, for example, those who generated/received cover-memos such as, in particular, the U.S. Reporting Officer responsible for "Global Pharmco-vigilance and Epidemiology." Why problems were "not serious" or reflected "tolerance to drug" cry for clarification. And why certain cases (including the instant-case) were recapitulated via submissions from the legal department is unclear, as is the apparent violation of confidentiality that was specifically manifest with regard solely to the instant-case [*see* **AVE 010526**].

Indeed, Aventis generated a letter that implied it had concluded "a lesser level of oversight was justified, notwithstanding the body of evidence accrued herein. It is, obviously, desirable to acquire all related correspondence, for the justification thereof must be compared/contrasted with the database. Essentially, despite not having pursued "leads" within the ADRs, Aventis sought the ability to gloss-over future submissions. Certainly, it will be vital to ensure that documentation is provided regarding the effort to "search existing data sources, gather and maintain the needed data, and review the data."

Although the laws governing FDA-activity [http://www.fda.gov/opacom/laws/] have not been extensively summarized herein, it is assumed that it transfers its internal criteria to the requirements of pharmaceutical houses which are being provided ADR reports. Thus, the "level of expectation" harbored by the public regarding FDA-level oversight is intuitively anticipated by the FDA to be honored by Aventis in the post-marketing arena.

Although discussion of the legalities and liabilities of such submissions is beyond the scope of this report, it is instructive to note that the 1997 FDA Modernization Act [http://www.fda.gov/cder/guidance/105-115.htm#SEC.%20420] contains a disclaimer that is clearly intended to dissuade corporations from fearing that liability-based litigation would inevitably follow any expression of candor. [This particular law was cited because its implementation-date clearly fell prior to events leading up to those in 2003.]

Consider [from "Subchapter G--Safety Reports"]:

<<NOTE: 21 USC 379v.>>
SEC. 756. SAFETY REPORT DISCLAIMERS.

> "With respect to any entity that submits or is required to submit a safety report or other information in connection with the safety of a product (including a product that is a food, drug, device, dietary supplement, or cosmetic) under this Act (and any release by the Secretary of that report or information), such report or information shall not be construed to reflect necessarily a conclusion by the entity or the Secretary that the report or information constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or otherwise caused or contributed to a death, serious injury, or serious illness. Such an entity need not admit, and may deny, that the report or information submitted by the entity constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or caused or contributed to a death, serious injury, or serious illness."

The FDA avers [http://www.fda.gov/cder/Offices/Biostatistics/ONeill_368/sld041.htm] that impediments to ADR-Reporting may relate to definitional concerns and the potential for imprecision to arise [with this reference from an on-line Power-Point presentation]. Yet, there is no evidence that such concerns were extant with regard to Lovenox. And there is extensive literature [http://www.fda.gov/medwatch/articles/medcont/ref.htm] that includes such ethical concerns as confidentiality (recalling the revelation of the name of the plaintiff in this matter, *vide supra*). [It is also noted that "ADR" can denote both "Adverse Drug Reaction" and "Authorized Distributor of Record" and, thus, the latter (e.g., http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0226-gdl0003.pdf) is ignored.]

Thus, the summary of its status in 2002 is particularly instructive as to the regulatory atmosphere extant prior to 2003 [http://www.fda.gov/oc/mcclellan/adverse.html], to wit:

Key Strategies

> FDA uses a risk-based approach to adverse event reporting that harmonizes efforts across the three medical centers (drugs, biologics and medical devices):
>
> 1. Establish Reporting Capability.
> 2. Develop analytical capability to identify and quantify medical product risk and to investigate, analyze and understand these risks and their consequences based on adverse information that is captured (risk analysis/assessment).
> 3. Increase communication of risks to educate both health professionals and patients about problems and solutions associated with appropriate product use (risk management decisions).

Although there are undoubtedly more "formalistic" presentation of this charge to the FDA and Aventis, this appears to encompass what is expected, expressed in lay-language [http://www.fda.gov/cder/handbook/adverse.htm] and employing the identical title […"Pharmaco-vigilance…"] that at least one Aventis employee touted [**AVE 010269**]:

Spontaneous Reporting System

> CDER's Division of Pharmacovigilance and Epidemiology (DES) maintains a Spontaneous Reporting System (SRS) which contains the adverse drug reaction reports from hospitals, health care providers and lay persons that are sent either directly to the Agency (via MEDWatch) or first to the drug manufacturer, and then, by regulation, to the Agency by the manufacturer.
>
> In the near future, SRS will be replaced by an expanded system called the Adverse Events Reporting System (AERS), currently under development. AERS is the result of efforts to implement many agreements from the International Conference for Harmonization (ICH) as well as new regulations and pharmacovigilance processes of the FDA to increase the efficiency with which CDER receives, files, and analyzes these reports. To learn more about AERS, visit CDER's AERS home page.
>
> These reports are triaged through the MEDWatch program, then forwarded to the appropriate Center (Drugs, Biologics, Foods or Veterinary). Adverse Drug Reaction Reports are also sent directly from the sponsors of the New Drug Application (NDA) to the Division. When either of these types of reports are received, they are entered into the computerized SRS.
>
> The SRS is maintained and used by DPE's data processing, epidemiology and statistic staff. ***Their efforts are aimed at actively analyzing the data through recognition of Adverse Drug Reaction (ADR) patterns that might indicate a public health problem (a "signal"). Improving access to the data facilitates our timely evaluation of aggregates of Adverse Drug Event (ADE) reports, which are often the first signals of a potential problem. The individual reports of serious adverse events are then critically and individually reviewed by staff trained in the analysis of these data and signal generation.*** DPE receives approximately 250,000 adverse experience reports possibly associated with drug use annually. Approximately 25% of the reports received by CDER are reports of serious and unlabelled (or 15-day) and/or Direct Reports.
>
> The primary focus of DPE's reviews is to detect serious unlabeled reactions. Adverse experience reports are reviewed and analyzed to generate signals of serious, yet unrecognized, drug-associated events.

> These signals are communicated within DPE to staff epidemiologists and to the relevant review division via written summaries and safety conferences.
>
> ***When DPE suspects that manufacturers have not been reporting ADRs as required, DPE prepares summaries of adverse drug experience reporting deficiencies and forwards this information to CDER's Office of Compliance, Division of Prescription Drug Compliance and Surveillance (DPDCS). Based on such information, DPDCS issues inspectional assignments to FDA field offices to follow-up these deficiencies at the pertinent firm. DPDCS evaluates the information provided by DPE along with the inspectional findings and makes a determination if further regulatory action is indicated.***
>
> In addition, DPE represents the Office of Epidemiology and Biostatistics on the Therapeutic Inequivalency Action Coordinating Committee (TIACC). DPE's representative assists in the investigation and resolution of claims of alleged drug bioinequivalency. In this way, CDER works to prevent injury from drugs that are super-potent or sub-potent because of manufacturing errors.

In light of the following, it will be necessary to review what Aventis filed with the FDA:

> ***Current Status***
>
> *Establish Reporting Capability* - FDA has developed and is improving a system of voluntary reporting of adverse events associated with the use of Agency-approved products. The Agency's MedWatch program receives about 25,000 adverse event and medical product problem reports annually, mostly from health care professionals and consumers. The MedWatch data are entered into FDA's Adverse Events Reporting System, which also receive 270,000 manufacturers' reports. ***The manufacturers' reports, which must be filed periodically, are based on information provided by physicians and other health care providers.***

To summarize this report through page 50, the concepts exhaustively detailed in the first report have been corroborated by having reviewed subsequently-acquired case-reports. When requested to confirm the issues being litigated in the instant case, the reasoning applied is both “deductive” and “inductive.” It can easily be deduced that there were ADRs which documented neonatal hemorrhage (CNS and/or elsewhere) and which were otherwise unexplained, not withstanding the broad assertion that Lovenox doesn’t cross the placenta. It can easily be induced that, knowing this fact and noting that Aventis apparently did absolutely nothing to explore the details of these ADRs, there was a “behavioral cover-up” that recalls the “hear no evil, see no evil, speak no evil” metaphor. Essentially, violating FDA guidelines, there was no “due diligence” effort to identify the etiology of hemorrhagic events affecting the fetus that occurred after Lovenox use.

Literature Review [#1]

Barjot, *et al*. reported ten (10) women with Factor V Leiden who had no complications of their pregnancies (either thrombosis or hemorrhage) following Lovenox [**AVE 004576**]. References were not provided, particularly #13 which was cited as support for the view that Lovenox doesn't cross the placenta. The use of anti-Xa was discussed, but no firm conclusion was drawn (following literature citation) regarding this or other testing.

Brenner, *et al*. reported fifty (50) women with thrombophilia who had an improved rate of successful pregnancies following Lovenox [**AVE 004587**]. There were two patients with hematologic complications, one hemorrhagic and one thrombotic. Anti-Xa was assessed in ten (10) women. Two women experienced thrombosis and one had bleeding, but no fetus was adversely affected at term, although spontaneous abortions had occurred.

The next article was preceded by an abstract that again noted the absence of any bleeding problem in the neonates [**AVE 004597**]; again, also, no blood test monitoring occurred:

LOW-MOLECULAR-WEIGHT HEPARIN IN PREGNANCY AND DELIVERY: EXPERIENCE WITH 24 CASES.

M. Dulitzki,* D.S. Seidman,* E. Sivan,* A. Horowitz,* G. Barkai,* E. Schiff. Department of Obstetrics and Gynecology, Sheba Medical Center, Tel-Aviv University, Israel.

BACKGROUND: Limited data are available regarding the use of low-molecular-weight heparin (LMWH), a fraction with high bioavailability and prolonged half-life, for antithrombotic therapy through pregnancy, labor and the different modes of delivery.

STUDY DESIGN: Descriptive study of the pregnancy and delivery course of 24 patients treated by subcutaneous (S.C.) injection of the LMWH enoxaparine (Rhone-Poulenc Rorer, France).

RESULTS: Twenty-four pregnant women, aged 20-38 years, were treated by 20-80 (median 40) mg/day of S.C. enoxaparine. Indications for therapy were thromboembolic event during pregnancy (33%), anti-phospholipid syndrome (33%), and active lupus disease (33%). Therapy was administered for 5 to 252 (median 91) days, and was continued through labor and the puerperium. No cases of systemic or local side effects and no thromboembolic events were reported. There was one case of first trimester bleeding which resolved spontaneously. Four midtrimester surgical procedures (1 cervical cerclage and 3 terminations of pregnancy due to worsening of lupus disease) were not associated with any significant bleeding. One out of 9 patients who underwent spontaneous vaginal delivery had increased postpartum hemorrhage with no need, however, for blood transfusion. Twelve patients underwent surgical deliveries (3 vacuum assisted and 9 cesarean deliveries), none of whom had abnormal bleeding during or following the surgical procedure. Furthermore, no case of hemoglobin concentration decline of >2 g% was reported. Neither bleeding disorders nor congenital anomalies were diagnosed in any of the newborns.

CONCLUSIONS: This preliminary series, although small, is the largest available in the literature and demonstrates the safety and efficacy of LMWH in pregnancy and delivery. Hence, LMWH may represents an advance in antithrombotic prophylaxis in obstetrics.

Casele, *et al*. assessed the pharmacokinetics of Lovenox in 13 pregnant women; it was noted that renal clearance was higher and, thus, a higher dosage was needed to ensure the anti-Xa activity had been affected [**AVE 004592**]. No adverse effect on the fetus was reported. These references supported the view that Lovenox does not cross the placenta:

2. Brancazio LR, Roperti KA, Stierer R, Laifer SA.Pharmacokinetics and pharmacodynamics of subcutaneous heparin during the early third trimester of pregnancy. Am J Obstet Gynecol 1995;173:1240-5.
3. Forestier F, Daffos F, Rainaut M, Toulemonde F. Low molecular weight heparin (CY 216) does not cross the placenta during the third trimester of pregnancy [letter]. Thromb Haemost 1987;57:234.
4. Omri A, Delaloye JF, Andersen H, Bachmann F. Low molecular weight heparin Novo (LHN-1) does not cross the placenta during the second trimester of pregnancy. Thromb Haemost 1989;61:55-6.

Gris, *et al*. reported 29 women who had taken Lovenox and who had experienced a higher rate of successful pregnancies than had those who had used Moroxidien Chloride; no neonatal hemorrhagic complications were reported with Lovenox [**AVE 004602**].

Nelson-Piersy, *et al*. reported 61 women who had taken Lovenox without neonatal hemorrhage; anti-Xa was checked and noted, but did not dictate dosage [**AVE 004608**].

Pajor, *et al*. reported 35 women who had taken Lovenox; four examined placentae had micro-/macro-scopic thromboses, a finding that was not analyzed [**AVE 004615**].

Younis, *et al*. reported 7 women who had taken Lovenox; there were two abortions and five normal live-births; no anti-Xa or placenta pathology was noted [**AVE 004526**].

Assessment: Although the focus of these reports was to report successful prophylaxis with Lovenox in women with thrombophilia, they included inconsistent information regarding the use of testing (anti-Xa) and pathology examination (placenta) while citing articles averring that Lovenox does not cross the placenta. This enhances the need, therefore, to assess the pharmacologic database that has been generated in this regard.

Correspondence [#2]

Edmond Roland, M.D. of Aventis (Senior Director, Regulatory Affairs) informed Lilia Talarico, M.D. of the FDA (Center for Drug Evaluation and Research) on 9/12/2000 that a review of all clinical data (1/1/1987 – 6/15/2000) failed to demonstrate any toxicity of Lovenox when administered during pregnancy [**AVE 004439**]. Attached to the letter was a summary-report that supported the claim that Lovenox does not cross the placenta by stating there was no anti-Xa activity. It reported 17 cases of Severe Adverse Effects upon the fetus and it included a summary of the basic science (referenced elsewhere).

Animal studies summarized therein demonstrated trans-placental effects. In rats, it was able to reach fetal cartilage. Although placental transfer appeared "restrictive," it existed; the level in fetal tissues was 1-10% that of maternal tissues. These are the details:

> The placental transfer, fetal tissue distribution and milk transference of ^{35}S-enoxaparin have been investigated in the female rat, following single subcutaneous and intravenous administration at a nominal dose level of 0.85 mg/kg body weight (85 IU anti-Factor Xa/kg body weight). The pattern of distribution in both maternal and fetal tissues appeared to be similar whether administered via the subcutaneous or intravenous dose route. Whole body autoradiography revealed that distribution of enoxaparin and/or metabolites was rapid and widespread throughout maternal tissues. Whole body autoradiography revealed that placental transfer of radioactivity was restricted and limited to fetal cartilage. Quantitative tissue distribution studies confirmed the findings of whole body autoradiography.
>
> Placental transfer of radioactivity appeared restrictive. Levels of radioactivity in fetal tissues were some 10 to 100 fold less than those associated with maternal tissues. The pattern of distribution appeared to be independent of dose route. Following administration of ^{35}S-enoxaparin to lactating rats, the potential for milk transference was very limited. Very low levels of radioactivity were detected in milk with a mean maximum concentration of 0.22 ± 0.55 µg equivalent per gram and 0.11 ± 0.10 µg equivalent per gram occurred after subcutaneous and intravenous administration respectively. Concentrations of radioactivity were near or below the limit of detection by 48 hours post-dose. Thus, placental and milk transfer following doses equivalent to those used for prophylaxis appear low and may not emphasize any evident risk in pregnant and breast feeding women.

In sheep, Lovenox induced release of an endogenous "dermatan sulfate"-like substance, which alters fetal coagulation; these fetal anticoagulant effects were only detectable after maternal administration of Lovenox, suggesting that the placenta contributed to the anticoagulant effect. This information is consistent with the aforementioned "clues" embedded within the case reports that had been painstakingly distilled and analyzed:

> In another study, also carried out in the pregnant sheep, it was shown that enoxaparin altered coagulation without crossing the placenta. To characterize this anticoagulant, in vitro and in vivo effects of enoxaparin were measured in maternal and fetal plasmas, following administration of enoxaparin to the mother or fetus. The fetal anticoagulant activity was not neutralizable by protamine sulphate and was attributable to the inhibition of thrombin but not factor Xa. In vitro, the fetal anticoagulant activity had properties similar to dermatan sulphate. These effects were due to the enhanced neutralization of thrombin by heparin cofactor II. It was concluded that enoxaparin does not cross the placenta, but it does induce the release of an endogenous dermatan sulphate-like substance which alters fetal coagulation. These fetal anticoagulant activities were only detectable after the administration of enoxaparin to the mother, suggesting that the placenta contributed to the anticoagulant effect.

Assessment: Aventis KNEW animal studies had DEMONSTRATED effects of Lovenox that were TRANS-PLACENTAL; nevertheless, these data were not then disseminated.

This is relevant background regarding Dermatan Sulfate:

> http://www.ncbi.nlm.nih.gov/pubmed/12213784
>
> **Trowbridge JM, Gallo RL., Dermatan sulfate: new functions from an old glycosaminoglycan.**
>
> Glycosaminoglycans constitute a considerable fraction of the glycoconjugates found on cellular membranes and in the extracellular matrix of virtually all mammalian tissues. Their ability to bind and alter protein-protein interactions or enzymatic activity has identified them as important determinants of cellular responsiveness in development, homeostasis, and disease. Although heparan sulfate tends to be emphasized as the most biologically active glycosaminoglycan, dermatan sulfate is a particularly attractive subject for further study because it is expressed in many mammalian tissues and it is the predominant glycan present in skin. Dermatan and dermatan sulfate proteoglycans have also been implicated in cardiovascular disease, tumorigenesis, infection, wound repair, and fibrosis. Growing evidence suggests that this glycosamino-glycan, like the better studied heparin and heparan sulfate, is an important cofactor in a variety of cell behaviors.

It must be emphasized that the above information constitutes the entire dataset provided in this FDA submission. Therefore, it is vital to determine how it was then processed.

This is a tabular-presentation summarizing the categories of adverse-effects on the fetus:

ADVERSE EVENTS IN MOTHER AND/OR FETUS / INFANT	NUMBERS OF CASES REPORTED
AE in fetus / neonate without an AE in mother	17+ 1 which is no longer an AE
Fetal deaths / abortions without an AE reported in mother	17
AE in mother leading to fetal death	12
AE in mother and fetus *(excluding fetal deaths)*	2
AE in mother without an AE in fetus/newborn	8
Total	**56**

The latter three groups are not of particular interest, and the second has been "preserved" as a potential concern noting—for example—the need to know placental pathology. Thus, the key in this case is to study those AE's that had a hemorrhagic component. Of the 17 such cases, there were 3 with purpura (with or without thrombocytopenia), 2 of which were not felt by the reporter to be Lovenox-related (because subsequent neonates also developed thrombocytopenia). There were an additional 3 cases of fetal distress not felt by the reporter to be Lovenox-related (with thrombocytopenia reported in one case, possibly felt to be Lovenox-related, associated with an adrenal hematoma); yet, of the remaining two cases, one had a possible cerebral hemorrhage (and DIC) causing hydrocephaly (while the other had cerebral atrophy, corpus callosum agenesis, fluid on the left side of the brain, and a dysmorphic appearance). And there was one case of intracerebral hemorrhage (with the others demonstrating other congenital abnormalities).

Therefore, of the 17 cases compiled from myriad studies, two had cerebral hemorrhage, another had adrenal hemorrhage, and three with thrombocytopenia causing petechiae (two of whom had recurrent thrombocytopenia). Because it cannot be assumed that these cases of persistent thrombocytopenia (a)—actually transpired, (b)—were determinative, it cannot be assumed that they did not have any relationship with Lovenox-usage. Thus, that there were as many as five cases with a primarily hemorrhagic complication is a finding that cannot be dismissed as happenstance or an isolated phenomenon.

Of the 17 cases with spontaneous fetal death or abortion, only one placenta was studied; here, again, although the case reports contained variable degrees of support for other etiologic forces (such as s/p automobile accident) and the spontaneous events were easily ascribed to the underlying thrombophilia (such as a previously-defined coagulopathy), knowing the basic science [*supra*] would mandate such a modicum of follow-up inquiry.

Of the 12 cases of maternal coagulopathies causing fetal demise, one was found to be retro-placental hemorrhage; again, not withstanding other distinct case-characteristics, examination of the placentae should have been requested and reported. In contrast, perhaps, the 2 cases of gestational hypertension had non-hemorrhagic fetal effects, and the 7 cases of purely-maternal adverse-events were clearly non-hemorrhagic in quality. Thus, the absence of a routine report of the placenta may have led to underreporting of Lovenox's potential to have triggered a coagulopathy that then caused complications.

Also, of the 9 cases of Lovenox-complications reported to the World Health Organization (1986 – 2000), there was "one neonatal adverse effect" (again left uncharacterized). The conclusion was that there was a paucity of cases that did not increase over time and that did not evidence any particular issue (mirroring Heparin) [AVE 004457-8]. Yet, the appendix contained a "Caveat Document" [AVE 004492] warning that interpretation of its data may be misleading due to numerous operational impediments, ending thusly:

> Any publication, in whole or in part, of the obtained information must have published with it a statement:
>
> (i) of the source of the information,
>
> (ii) that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction,
>
> (iii) that the information does not represent the opinion of the World Health Organization.
>
> **Omission of these 3 statements may exclude the responsible person or organization from further information from the system.**

These 3 statements were explicitly omitted from the text of the Aventis-authored report.

Assessment. The absence of intellectual curiosity is apparent when investigators draw conclusions without having acquired data which would impact on their decision-making. It is granted that the ability to trace-back the W.H.O. cases might be limited (although the ability to acquire quality data diminished rapidly when even short time-periods passed). But the other bleeding cases were addressed dismissively, instead of analyzed cogently. And the gross/overt anti-scientific bias of the authors of this report was evidenced by their having ignored the mandate that citation of W.H.O. data contain a key disclaimer.

Reports ("spontaneous" and "study") were provided. Because the numbering-system does not comport with that which had been employed within internal Aventis documents, it is not possible to cross-ruff these data, let alone confirm the completeness of either set. Key information gleaned selectively from these précises cannot supplant more extensive review comprehensively tethered to the cases analyzed *supra*, compared and contrasted.

FR02-00777 (1993) depicted fetal death from a completely infarcted placenta. Yet, discussion of this case was not noted in the text of the Aventis-composed report.

FR02-00825 (1993) depicted fetal death associated with "six infarcted areas of varying age present in the placenta which are routinely observed in so-called unexplained intrauterine death." On the one hand, this observation may be off-putting; on the other hand, however, it reflects review of placental pathology that is lacking elsewhere.

FR0201761 (1995) depicts possible neonatal Evans Syndrome (hemolytic anemia and thrombocytopenia) associated with hemorrhage; the thrombocytopenia was felt to be "possibly due to Lovenox" despite the absence of maternal thrombocytopenia. Again, information from the placental pathology might have explained/linked these findings, noting the negative Coombs test; the thrombocytopenia might have been "secondary."

US01-24145 (2000) depicts a newborn with intraventricular hemorrhage. It is unclear why the reporting physician did not link this event with prior use of Lovenox.

HU01-00004 (2000) depicts a woman who had a second-trimester induced abortion following partial separation of the placenta and, subsequently, a third-trimester induced abortion associated with thrombocytopenia; on both occasions, the placenta showed microinfarcts and macroinfarcts. No impression was provided as to the etiology of these events, other than to have noted the maternal history of antiphospholipid antibody. [This is the Hungarian case discussed on page #90 of this physician's initial Expert Letter.]

HU01-00005 (2000) depicts another Hungarian case in which the placenta demonstrated microinfarcts and macroinfarcts. Many key-details are otherwise not provided.

HU01-00009 (2000) depicts another Hungarian case in which thrombocytopenia was linked to fetal death at 21-weeks' gestation. Again, further details were not available.

Assessment: These "spontaneous" reports corroborate aforementioned links among Lovenox, placental thrombosis, and fetal/neonatal hemorrhage (often intracerebral).

The Study Reports focus on spontaneous abortion/miscarriage and the association with valvular replacement. In none of these dozen cases was there a report on the status of the placental pathology, except that the last case documented hemorrhagic/necrotic deciduas.

Assessment: Obviously, "the numbers simply don't add-up." Specifically, the database in the article does not comport with the information in the Appendix, and it is simply impossible to attempt to try to correlate the cases based on such sparse information. And the "Table of Case Summaries" does not provide any further substantive guidance, nor does the "Line Listing of Adverse Events in Pregnant Women"; in both instances, information provided in an abbreviative format is devoid of pathological information (although, somewhat gratefully, homology of the internal numbering system exists).

Nine publications were studied, but none was felt to impact upon prior conclusions. Omitted, however, was discussion of articles that demonstrated overlapping concerns regarding other low-molecular-weight Heparin derivatives. Indeed, it is unclear whether the basic science findings noted herein were specifically addressed by the FDA and/or communicated (in)directly to the other known-to-be-involved pharmaceutical houses.

In the Appendix, the tabular presentation thereof mirrors points made *supra* [pp. 50-51] as to the contents of these articles. The subsequent database search included snippets of information corroborative of the above observation, which supports the view that the innate capacity for (if not avid encouragement of) information-sharing was not honored.

AVE 004511 depicts the approach to (and results of) this literature review, to wit:

NUMBER OF REFERENCES: 59
We conducted a systematic review, with MEDLINE and Cochrane Library data base searches and bibliographic reviews, of English-language reports describing therapy with low-molecular-weight heparin (LMWH) in *pregnancy*. Altogether 40 citations, excluding abstracts, were identified. When the quality of evidence was categorized according to the method outlined by the U.S. Preventive Services Task Force, 2 articles were level I, 3 were level II-1, 3 were level II-2, 4 were level II-3, 9 were level III, and the remaining 19 were classified as other (i.e., below level III). Of the 728 *pregnant* women and 1 postpartum woman described in the 40 citations, 340 (47%) received dalteparin, 192 (26%) *enoxaparin*, 108 (15%) certoparin, 54 (7%) *nadroparin* , 30 (4%) other LMWH, and 6 (< 1%) unspecified. The indication for LMWH in most patients (606 *pregnancies*, 83%) was for thromboprophylaxis. Daily doses ranged from 2500-22,000 U for dalteparin, 20 mg (2000 U)-80 mg (8000 U) for *enoxaparin*, 3000 U for certoparin, and 2050'15,000 U for *nadroparin*. Regimens included fixed dosages, increasing dosages as *pregnancy* progressed, dosages based on body weight, and dosages titrated according to anti-Xa levels. Duration of therapy ranged from a single dose to 476 days. Maternal anti-Xa levels were reported for 255 *pregnancies* . Target anti-Xa levels ranged from 0.1-0.6 U/ml and measured values from 0.0-0.7 U/ml. Major maternal findings were 18 local and generalized skin reactions, 27 bleeding complications, 9 thromboembolic events, 8 deep vein thromboses, 1 bilateral renal vein thrombosis, 4 pulmonary eraboli, 1 hepatic infarction, 4 cases of thrombophlebitis, 12 cases of preeclampsia, 1 placental abruption, and 2 osteoporotic vertebral fractures. A major fetal finding was lack of anti-Xa activity in fetal or cord blood. Published experience suggests that LMWHs are generally safe and effective when administered for thromboprophylaxis during *pregnancy*. Until prospective, randomized, controlled trials comparing them with unfractionated heparin are performed, their benefits in *pregnancy* will remain inconclusive.

AVE 004506 depicts a case in which anti-Xa testing occurred on four occasions at variable times during the pregnancies. This structure could not reasonably provide any reasonable recommendation regarding the use of this (or any other) such testing.

AVE 004514 notes *inter alia* that anti-Xa levels were not detectable either in the fetus or in the cord blood (following administration of a number of LMWH agents).

Assessment: Although not a major focus of discussion thus far in these analyses, discussion of how one might choose an optimal specific test must be studied with some precision in light of the results of the animal studies [*vide supra*]. The prominent test (whenever employed) was the anti-Xa (consistently throughout the medical literature), despite the availability of others [detailed in the first Expert Report] that might have been employed to reflect the Lovenox activity with greater precision. Because of the lack of any protocol-testing of these possibilities over the years, such analysis is not possible.]

AVE 004508 notes existence (in 2000) of four types of low-molecular-weight Heparin.

AVE 004553 notes existence (in 2000) of seven types of low-molecular-weight Heparin.

AVE 004518 focuses specifically on Fragmin (dalteparin), noting no complications.

AVE 004547 focuses specifically on Fragmin (dalteparin), noting no complications.

AVE 004535 depicts the safe use of Clexane (enoxaparin) in pregnancy, with specific reference to the absence of neonatal intraventricular hemorrhage. [This suggests that awareness of this concern with Lovenox was harbored by "competing" investigators.]

[Many foreign-language abstracts were incompletely provided via English-translation. Thus, although an effort is being made here to detect "clues" as to what was known (and by whom) regarding the potential for neonatal hemorrhage to occur in these women (with or without monitoring), it is possible for an industrious investigator to pull each of these articles to ensure nothing crucial has been embedded therein (that may not have been captured in a title or brief abstract or even a super-brief conceptual-summary).]

Assessment: Thus, all the competitors were both self-aware and capable (prior to 2003) of monitoring the events affecting this entire family of agents; such literature reviews need not have been initiated solely when a comprehensive report was being prepared.

Overall [Interim] Assessment: It is clear that a "smoking-gun"-type of document exists, here, documenting not only awareness of the potential for Lovenox to cause neonatal hemorrhage, but also knowledge of the putative pathogenesis of this complication. Nevertheless, a reasonable "Informed Consent" discussion would necessarily address the potential for a "cost:benefit" analysis to be conducted cogently, and repetitively. Also, had the Basic Science information been applied to testing, others that may have been less dependent on anti-Xa may have been developed and validated…and proven useful, thereby providing another dimension to the ongoing Informed Consent process.

Pregnancy Study Clinical Narratives [#3]

Terse case-summaries are provided of neonatal hemorrhage (AVE 004988 – 0045005) followed by major congenital abnormalities (which could also be due to Lovenox-effect); only the former are summarized herein, again recognizing the potential for data-overlap.

AVE 004988 depicts neonatal cephalhematoma.

AVE 004989 depicts multiple (external) neonatal hematomas.

AVE 004990 depicts neonatal hyaline membrane disease.

AVE 004991 depicts the birth of triplets, one of whom had a subependymal hemorhage.

AVE 004993 depicts a neonate who suddenly died on his 10th day of life.

AVE 004995 depicts multiple (external) neonatal hematomas.

AVE 004996 depicts neonatal eccymoses and petechiae.

AVE 004997 depicts neonatal prematurity (primarily pulmonary) and early death.

AVE 004998 depicts neonatal (ventricular and pulmonary) hemorrhage associated with a coagulopathy (thrombocytopenia and deficiency in Vitamin K-dependent cascade), followed by early death; it appears the coagulopathy was the major initial event.

Assessment: This case resembles others but, regardless, it reflects the potential for a process that initially was intrauterine to become manifest prominently, post-partum.

AVE 004999 depicts a mother who developed *abruptio placentae* who had a twin-birth; one daughter developed *inter alia* neonatal intraventricular hemorrhage.

Assessment: Although it appears that this pathological change (just as does HIT or the history of a cardiac valve replacement) could explain the sequellae, this does not obviate the potential for Lovenox (alone or as a contributory factor) to have played a role in the pathogenesis of what transpired; this concept is also applicable to many other cases.

AVE 005002 depicts neonatal intraventricular hemorrhage and excess intracerebral fluid, associated with moderate bronchopulmonary dysplasia and *E. Coli* septicemia.

Assessment: This is another case in which a detailed examination of the records would provide enlightenment as to the sequence-of-events; for example, the dysplasia suggests a primary congenital event, whereas the hemorrhage could have been mutually exclusive.

AVE 005003 depicts neonatal/maternal *Hemophilus Influenzae* septicemia associated with massive bilateral intracerebral hemorrhage and early death.

Assessment: This is another case in which a detailed examination of the records would provide enlightenment as to the sequence-of-events; for example, the sepsis suggests a peri-partum event, whereas the hemorrhage could have been mutually exclusive.

AVE 005004 depicts neonatal anemia due to ruptured vessel of the chorionic plate abnormally located on the amniotic membranes; also noted was thrombocytopenia (86K) plus bloody nasotracheal aspiration and microscopic hematuria [probably unrelated].

Pregnancy Clinical Study [#4]

AVE 004748 depicts (in tabular form) 13 cases of neonatal hemorrhage. It appears to mirror the case reports summarized *supra*; thus, until provided with a cross-referencing system that accommodates all of the cases from disparate sites, further analysis here has been deferred. Nothing unique appears to be noted in this clinical portrayal.

AVE 004818 depicts a protocol employed to assess clinical data. All hemorrhagic events were to be preserved, and the investigators opinion as to causality was to be recorded "for each event." This level of academic rigor was not applied, apparently, to the ADRs.

Assessment: The work-sheets regarding fetal hemorrhage were not provided.

AVE 004830 depicts creation of a Scientific Committee (apparently based in France), but none of the 1998 meetings focused on any of the Basic Science literature (per Minutes).

Assessment: The Minutes of subsequent meetings must be scrutinized.

Summary

A comprehensive, exhaustive review of the entire database has (finally!) been completed.

The major findings in the Aventis filing to the FDA were emphasized *supra*, to wit:

> A "smoking-gun"-type of document documents not only awareness of the potential for Lovenox to cause neonatal hemorrhage, but also knowledge of the putative pathogenesis of this complication. Nevertheless, a reasonable "Informed Consent" discussion would necessarily address the potential for a "cost:benefit" analysis to be conducted cogently, and repetitively. Also, had the Basic Science information been applied to testing, others that may have been less dependent on anti-Xa may have been developed and validated…and proven useful, thereby providing another dimension to the ongoing Informed Consent process.

Furthermore, a letter from Aventis (incredulously) attempted to evade FDA oversight:

> This letter implies that Aventis was seeking confirmation that a lesser level of oversight was justified, notwithstanding the body of evidence accrued herein. It is desirable to acquire all related correspondence, for the justification thereof must be compared/contrasted with the database. Despite not having pursued "leads" within the ADRs, Aventis sought the ability to gloss-over future submissions. It will be vital to ensure that documentation is provided regarding the effort to "search existing data sources, gather and maintain the needed data, and review the data."

The review of data generated from 2003-2007 yielded these conclusions:

> Thematic herein as been the dyad of problematic data and the lack of follow-up thereof. The former conclusion was confirmed when numerous cases related to neonatal bleeding were identified, and the latter conclusion was confirmed when numerous cases of issues that could be problematic were not pursued. Indeed, regarding the former, when the concept of transplacental passage could be entertained, cases were amazingly on-point relative to the instant case; indeed, regarding the latter, when the capacity to request such follow-up had been demonstrated elsewhere, the absence of inquiry was glaring.
>
> The mistaken impression could be drawn that a generic level of concern was created when those responsible for oversight (FDA/Aventis) did not show evidence of doing so; rather, it was the specific focus on such documented concerns as placental pathology that animates this concern. The same is true with anti-Xa testing and myriad cases of abortion/ miscarriage/premature-labor.
>
> That those who submitted the forms never checked-off the initial impressions drawn is another area of concern. Tracing how these issues were addressed internally by Aventis will necessarily trace how internal memos were translated into policy by, for example, those who generated/ received cover-memos such as, in particular, the U.S. Reporting Officer responsible for "Global Pharmco-vigilance and Epidemiology." Why problems were "not serious" or reflected "tolerance to drug" cry for clarification. And why certain cases (including the instant-case) were recapitulated via submissions from the legal department is unclear, as is the apparent violation of confidentiality that was specifically manifest with regard solely to the instant-case.

This segued into an expanded discussion of statutes derivative of the Food, Drug and Cosmetics Act, yielding the view that the FDA was tasked with ensuring that the input provided by "Big Pharma" comport with its Public Health mission. Indeed, it was shown that the more updated Congressional mandates served to tighten these responsibilities.

An interim decision summarizing key-concepts in the first 50 pages of this report was:

> When requested to confirm the issues being litigated in the instant case, the reasoning applied is both "deductive" and "inductive." It can easily be deduced that there were ADRs which documented neonatal hemorrhage (CNS and/or elsewhere) and which were otherwise unexplained, not withstanding the broad assertion that Lovenox doesn't cross the placenta. It can easily be induced that, knowing this fact and noting that Aventis apparently did absolutely nothing to explore the details of these ADRs, there was a "behavioral cover-up" that recalls the "hear no evil, see no evil, speak no evil" metaphor. Essentially, violating FDA guidelines, there was no "due diligence" effort to identify the etiology of hemorrhagic events affecting the fetus that occurred after Lovenox use.

As noted on page 10 [*supra*], the motives of Aventis employees have been questioned, although the conclusions drawn herein are not dependent upon this type of postulate.

At this point, the last four datasets were addressed, starting with the literature review:

> Although the focus of these reports was to report successful prophylaxis with Lovenox in women with thrombophilia, they included inconsistent information regarding the use of testing (anti-Xa) and pathology examination (placenta) while citing articles averring that Lovenox does not cross the placenta. This enhances the need, therefore, to assess the pharmacologic database that has been generated in this regard.

Then, in an FDA-filing by Aventis, a "smoking-gun" memo was unearthed that served to clarify the conduct of this pharmaceutical house. Essentially, Aventis has strategized that "stopping short" at the claim that Lovenox doesn't cross the placenta was sufficient to maintain its marketing towards the high-risk pregnancy patient population, to wit:

> Animal studies summarized therein demonstrated trans-placental effects. In rats, it was able to reach fetal cartilage. Although placental transfer appeared "restrictive," it existed; the level in fetal tissues was 1-10% that of maternal tissues.
>
> In sheep, Lovenox induced release of an endogenous "dermatan sulfate"-like substance, which alters fetal coagulation; these fetal anticoagulant effects were only detectable after maternal administration of Lovenox, suggesting that the placenta contributed to the anticoagulant effect. This information is consistent with the aforementioned "clues" embedded within the case reports that had been painstakingly distilled and analyzed.
>
> Aventis knew animal studies had demonstrated effects of Lovenox that were trans--placental; nevertheless, these data were not then disseminated.

Case reports were again summarized, both in this FDA filing and in the one to follow. In-between, an unequivocal ethical violation was ID'ed, accompanied by a postulated rationale for how it had occurred (within the context of the atmosphere extant at Aventis):

> The absence of intellectual curiosity is apparent when investigators draw conclusions without having acquired data which would impact on their decision-making. It is granted that the ability to trace-back the W.H.O. cases might be limited (although the ability to acquire quality data diminished rapidly when even short time-periods passed). But the other bleeding cases were addressed dismissively, instead of analyzed cogently. And the gross/overt anti-scientific bias of the authors of this report was evidenced by their having ignored the mandate that citation of W.H.O. data contain a key disclaimer…[from] a "Caveat Document" warning that interpretation of its data may be misleading due to numerous operational impediments…."Omission of these three statements [which transpired] may exclude the responsible person or organization [here, Aventis] from further information from this system."

It must be recalled that the information provided in these two Expert Letters was written *seriatim* as the relevant data were being analyzed; the only editing of the first letter that occurred, therefore, was to follow the same pattern when composing summary sections (thereby using "Distillation of Distillations" in like fashion, first in this letter and second in the initial letter). That is why the postulate of placental pathology was so crucial for, somewhat definitively, it was corroborated in the Aventis filing reviewed subsequently.

Finally, the case-reports in the latter three data-sets generated a few worthy distillations:

Assessment: These "spontaneous" reports corroborate aforementioned links among Lovenox, placental thrombosis, and fetal/neonatal hemorrhage (often intracerebral).

Assessment: Obviously, "the numbers simply don't add-up." Specifically, the database in the article does not comport with the information in the Appendix, and it is simply impossible to attempt to try to correlate the cases based on such sparse information. And the "Table of Case Summaries" does not provide any further substantive guidance, nor does the "Line Listing of Adverse Events in Pregnant Women"; in both instances, information provided in an abbreviative format is devoid of pathological information (although, somewhat gratefully, homology of the internal numbering system exists).

Assessment: Although not a major focus of discussion thus far in these analyses, discussion of how one might choose an optimal specific test must be studied with some precision in light of the results of the animal studies [*vide supra*]. The prominent test (whenever employed) was the anti-Xa (consistently throughout the medical literature), despite the availability of others [detailed in the first Expert Report] that might have been employed to reflect the Lovenox activity with greater precision. Because of the lack of any protocol-testing of these possibilities over the years, such analysis is not possible.]

Assessment: Thus, all the competitors were both self-aware and capable (prior to 2003) of monitoring the events affecting this entire family of agents; such literature reviews need not have been initiated solely when a comprehensive report was being prepared.

Assessment: This case resembles others but, regardless, it reflects the potential for a process that initially was intrauterine to become manifest prominently, post-partum.

Assessment: Although it appears that this pathological change (just as does HIT or the history of a cardiac valve replacement) could explain the sequellae, this does not obviate the potential for Lovenox (alone or as a contributory factor) to have played a role in the pathogenesis of what transpired; this concept is also applicable to many other cases.

Assessment: This is another case in which a detailed examination of the records would provide enlightenment as to the sequence-of-events; for example, the dysplasia suggests a primary congenital event, whereas the hemorrhage could have been mutually exclusive.

Assessment: This is another case in which a detailed examination of the records would provide enlightenment as to the sequence-of-events; for example, the sepsis suggests a peri-partum event, whereas the hemorrhage could have been mutually exclusive.

Assessment: The work-sheets regarding fetal hemorrhage were not provided.

Assessment: The Minutes of subsequent meetings must be scrutinized.

Assessment of Assessments: More clarifying information is needed from Aventis as to the identity of patients who had ADRs, allowing for the contrast of renditions in various fora. In addition, the dearth of data as to lab testing (beyond anti-Xa) reflects the consequences of perpetuation of the false claim of safety in pregnancy without the need for monitoring. The lack of multifactorial forces was addressed in numerous ways, and the need for the data upon which Aventis made decisions (work sheets, meeting minutes, etc.) was noted.

Summary of Summaries

The points made in the first and last sections of this Expert Report "sandwich" more data that corroborate the accusations issued somewhat empirically, perhaps, in the Complaint, for the detailed information in these two Expert Letters had yet to be articulated. Here, the bill-of-particulars was somewhat empiric, somewhat intuitive, somewhat imaginative. Yet, it was also a brilliant projection of the factual foundation of the case, as it developed. Merely the process of preparing the information for this physician's review created the subjective awareness of a profound problem that was then to be objectively proven. In any case, implicitly/explicitly the key-conclusion drawn while preparing these letters has been the fact that ***Aventis knew a decade ago that Lovenox caused a trans-placental anti-coagulant fetal effect and that—through inaction and obfuscation (claiming the molecule was too large to cross the placenta—tried to cover-up these data***. Emphasized again is the fact that this conclusion was derived from a "linear" review of the dataset.

Personal Statement

This physician embarked a month ago on the task of composing an Expert Report regarding an unfortunate incident that had occurred a half-decade ago. The capacity to review bulk information was not daunting, but it had to be approached incrementally. Indeed, the final-four-folders were not actually made available until this second Report had been initiated (following the decision to assess the ADRs filed after the incident). Furthermore, when an issue arose about which background information was needed, interrupting the narrative-flow permitted interim-remarks to be written with confidence. This, in turn, yielded the ability to maintain air-tight credibility while creating "context."

This unorthodox approach to composing a commentary was consistent with the views harbored by the plaintiff and her attorneys although, candidly, it had to be "discovered" through this somewhat laborious process; as Ms. Hill remarked [paraphrased], "I knew something vital was buried in those binders, but it took a medical-mind to unearth it." It is for this reason that insertions that appeared to resemble "stage directions" were made (such as statements regarding the mindset adopted when structuring the ADR-review), thereby empowering the reader to "fact-check" the **cases** and the *assessments* thereof. Again, Ms. Hill and her attorneys basically sat-back and watched the data emerge.

It has been recognized throughout that this case could carry tremendous implications. Furthermore, it is appreciated that a lengthy submission of this sort carries tremendous opportunity for cross-examination that most attorneys would eschew (tactically). Yet, there is an air-tight quality to this workman-like effort that is intended to ensure that any disinterested reader would concur with its incrementalism when, for example, the ADRs were distilled, assessed as individual entities, reassessed in groups, and then probed for implications (both regarding the conduct of Aventis and the oversight of the FDA).

It is anticipated that these reports (266 pages in length)—and/or excerpts thereof—will be shared with the defendants prior to the filing of any litigation, recognizing that the proper legal posture would be that ***false-marketing led to the creation of a confidence-level that led to the prescription of Lovenox in a pregnant woman without worriment about the potential for fetal hemorrhage to transpire and without the need to monitor its dosage***; that delay in the performance of a Caesarian section enhanced the risk-of-harm is noted, although separate filing of a formal opinion regarding this management is expected.

The myriad implications of this conclusion are inescapable, rippling through the FDA and the other pharmaceutical houses that manufacture low-molecular-weight Heparin. Of course, the task of reviewing data comparable to that supplied by Aventis would be pursued by this physician upon-request, although it may very well be facilitated by the use of these Expert Reports as "road-maps" as to how to unearth (assuming it is extant) the information which would implicate these other entities in a massive PR-blunder. Clearly, the onus falls on those who knew (or should have known) of the contents of the "smoking-gun" memo filed by Aventis with the FDA…and who failed to act thereupon. Perhaps it should not have necessitated the expenditure of sufficient energies to have composed a book-length, two-part monograph to achieve this, but this is where we are.

Executive Summary

Savannah Hill suffered perinatal intracerebral hemorrhage following Lovenox exposure, necessitating lifelong special-needs care after the development of permanent damages. These events occurred in 2003, three years after Aventis (the manufacturer of Lovenox) filed a report to the FDA that had cited the capacity of this agent to alter fetal coagulation in sheep by the induced release of an endogenous "dermatan sulfate"-like substance.

It appears that the body of literature that had been developed regarding dosage-testing had experienced a sudden halt (for whatever reason) following dissemination of data suggesting this agent was so safe that it could not even cross the placental barrier. Ignored also were numerous reports of placental pathology which suggested the fact that the sheep-data were reflecting what was being experienced by other mammals, humans.

The one counter-argument to all of this information that could be conjured by Aventis would be that the vast majority of pregnant women benefitted from the increased fertility (and decreased thrombophilia-risk) afforded by the use of Lovenox and that, therefore, Ms. Hill would have chosen to have been exposed to this agent even had she known that it might affect the fetus. This "Informed Consent" posture fails on two pivotal levels. *First*, within the "microcosm" of the clinical setting, she may very well have chosen not to risk the health of her child, accepting greater personal risk of experiencing phlebitis (plus any complication thereof). *Second*, within the "macrocosm" of the business setting, awareness of this trans-placental effect would reasonably have triggered Aventis to embark on a more concerted effort (indeed, ANY effort) to determine whether advising use of focused testing (of whatever type) might have been able to minimize this risk.

In many respects, it is anticipated that these two reports will serve to simplify the tasks that now must be tackled. For example, both the basic-science postulates (e.g., IgG) and the obstetrical concerns (e.g., whether delay caused damages) can be easily simplified; Aventis has supplied an articulation of the pathogenesis of what transpired, and the delay merely increased the risk that the intracerebral hemorrhage would cause lifelong harm.

Finally, it is recognized that articulating these extended-opinions may not resonate well within the legal minds to whom these Expert Reports have been remitted. But they are provided because a reasonable effort must be made to probe what would likely transpire in the community setting when patients such as Ms. Hill were to confront such concerns.

If any further analysis/discussion is needed, please do not hesitate to call.

Sincerely,